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# UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	5/1275
First Inventor	Armin HECKEL
Title	Substituted Indolines Which Inhibit Receptor Ty
Express Mail Label No.	EL515660737US

## APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

- ☒ Fee Transmittal Form (e.g., PTO/SB/17)  
(Submit an original and a duplicate for fee processing)
- ☐ Applicant claims small entity status.  
See 37 CFR 1.27.
- ☒ Specification [Total Pages 267]  
(preferred arrangement set forth below)
  - Descriptive title of the invention
  - Cross Reference to Related Applications
  - Statement Regarding Fed sponsored R & D
  - Reference to sequence listing, a table, or a computer program listing appendix
  - Background of the Invention
  - Brief Summary of the Invention
  - Brief Description of the Drawings (if filed)
  - Detailed Description
  - Claim(s)
  - Abstract of the Disclosure
- ☐ Drawing(s) (35 U.S.C. 113) [Total Sheets ☐
- Oath or Declaration [Total Pages ☐]
  - ☐ Newly executed (original or copy)
  - ☐ Copy from a prior application (37 CFR 1.63 (d))  
(for continuation/divisional with Box 17 completed)
    - ☐ **DELETION OF INVENTOR(S)**  
Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
- ☐ Application Data Sheet. See 37 CFR 1.76

ADDRESS TO: Assistant Commissioner for Patents  
Box Patent Application  
Washington, DC 20231

- ☐ CD-ROM or CD-R in duplicate, large table or Computer Program (Appendix)
- Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary)
  - ☐ Computer Readable Form (CRF)
  - Specification Sequence Listing on:
    - ☐ CD-ROM or CD-R (2 copies); or
    - ☐ paper
  - ☐ Statements verifying identity of above copies

## ACCOMPANYING APPLICATION PARTS

- ☐ Assignment Papers (cover sheet & document(s))
- ☐ 37 CFR 3.73(b) Statement of Power of Attorney  
(when there is an assignee)
- ☐ English Translation Document (if applicable)
- ☐ Information Disclosure Statement (IDS)/PTO-1449
- ☐ Preliminary Amendment
- ☒ Return Receipt Postcard (MPEP 503)  
(Should be specifically itemized)
- ☐ Certified Copy of Priority Document(s)  
(if foreign priority is claimed)
- ☐ Other: .....

17. If a CONTINUING APPLICATION, check appropriate box, and supply the requisite information below and in a preliminary amendment, or in an Application Data Sheet under 37 CFR 1.76:

☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP)

of prior application No.: .....

Prior application information:

Examiner: .....

Group / Art Unit: .....

For CONTINUATION OR DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 5b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

## 18. CORRESPONDENCE ADDRESS

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Name (Print/Type)	Alan R. Stempel	Registration No. (Attorney/Agent)	28,991
Signature	<i>Alan R. Stempel</i>	Date	10/03/00

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# FEE TRANSMITTAL for FY 2000

Patent fees are subject to annual revision.

TOTAL AMOUNT OF PAYMENT

(\$ 980.00)

## Complete if Known

Application Number	To Be Accorded
Filing Date	10/03/00
First Named Inventor	Armin HECKEL
Examiner Name	
Group Art Unit	
Attorney Docket No.	5/1275

## METHOD OF PAYMENT (check one)

1. ☒ The Commissioner is hereby authorized to charge indicated fees and credit any overpayments to:

Deposit Account Number 02-2955  
 Deposit Account Name

- ☒ Charge Any Additional Fee Required Under 37 CFR 1.16 and 1.17

☐ Applicant claims small entity status. See 37 CFR 1.27

2. ☐ Payment Enclosed:

☐ Check ☐ Credit card ☐ Money Order ☐ Other

## FEE CALCULATION

## 1. BASIC FILING FEE

## Large Entity Small Entity

Fee Code	Fee (\$)	Fee Code	Fee (\$)	Fee Description	Fee Paid
101	690	201	345	Utility filing fee	710.00
106	310	206	155	Design filing fee	
107	480	207	240	Plant filing fee	
108	690	208	345	Reissue filing fee	
114	150	214	75	Provisional filing fee	

SUBTOTAL (1) (\$ 710.00)

## 2. EXTRA CLAIM FEES

Total Claims	Extra Claims	Fee from below	Fee Paid
20	-20** = 0	18.00	0.00
2	-3** = 0	80.00	0.00
Multiple Dependent		270.00	270.00

\*\*for number previously paid, if greater; For Reissues, see below

## Large Entity Small Entity

Fee Code	Fee (\$)	Fee Code	Fee (\$)	Fee Description
103	18	203	9	Claims in excess of 20
102	78	202	39	Independent claims in excess of 3
104	260	204	130	Multiple dependent claim, if not paid
109	78	209	39	** Reissue independent claims over original patent
110	18	210	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) (\$ 270.00)

## FEE CALCULATION (continued)

## 3. ADDITIONAL FEES

## Large Entity Small Entity

Fee Code	Fee (\$)	Fee Code	Fee (\$)	Fee Description	Fee Paid
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for <i>ex parte</i> reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	380	216	190	Extension for reply within second month	
117	870	217	435	Extension for reply within third month	
118	1,360	218	680	Extension for reply within fourth month	
128	1,850	228	925	Extension for reply within fifth month	
119	300	219	150	Notice of Appeal	
120	300	220	150	Filing a brief in support of an appeal	
121	260	221	130	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive - unavoidable	
141	1,210	241	605	Petition to revive - unintentional	
142	1,210	242	605	Utility issue fee (or reissue)	
143	430	243	215	Design issue fee	
144	580	244	290	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Petitions related to provisional applications	
126	240	126	240	Submission of Information Disclosure Stmt	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	690	246	345	Filing a submission after final rejection (37 CFR § 1.129(a))	
149	690	249	345	For each additional invention to be examined (37 CFR § 1.129(b))	
179	690	279	345	Request for Continued Examination (RCE)	
169	900	169	900	Request for expedited examination of a design application	

Other fee (specify) \_\_\_\_\_

\* Reduced by Basic Filing Fee Paid

SUBTOTAL (3) (\$)

## SUBMITTED BY

Name (Print/Type)

Alan R. Stempel

Registration No.

28,991

## Complete (if applicable)

Telephone

203/798-4868

Signature

Date

10/03/00

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SUBSTITUTED INDOLINES WHICH INHIBIT RECEPTOR TYROSINE KINASES

Related Applications

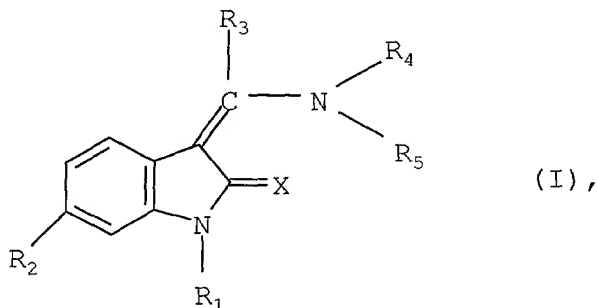
5 Benefit of U.S. Provisional Application Serial No. 60/160,547, filed on October 20, 1999, is hereby claimed.

Field of the Invention

10 The present invention relates to novel indolinones that inhibit receptor tyrosine kinases, their use as pharmaceuticals, particularly in the treatment of proliferative diseases, and pharmaceutical compositions comprising these compounds.

Description of the Invention

15 The present invention provides new indolinones of general formula



20 substituted in the 6 position, the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof, particularly the physiologically acceptable salts thereof which have valuable properties.

The above compounds of general formula I wherein R<sub>1</sub> denotes a hydrogen atom or a prodrug group have valuable pharmacological properties, in particular an inhibiting effect on various kinases, especially receptor tyrosine kinases such as VEGFR2, PDGFR $\alpha$ ,  
25 PDGFR $\beta$ , FGFR1, FGFR3, EGFR, HER2, IGF1R and HGFR, as well as complexes of

CDK's (Cyclin Dependent Kinases) such as CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK8 and CDK9 with their specific cyclins (A, B1, B2, C, D1, D2, D3, E, F, G1, G2, H, I and K) and to viral cyclin (cf. L. Mengtao in J. Virology 71(3), 1984-1991 (1997)), and on the proliferation of cultivated human cells, in particular endothelial cells,  
5 e.g. in angiogenesis, but also on the proliferation of other cells, in particular tumour cells.

The other compounds of the above general formula I wherein R<sub>1</sub> does not denote a hydrogen atom or a prodrug group are valuable intermediate products for preparing the  
10 abovementioned compounds.

The present invention thus relates to the above compounds of general formula I, whereby those compounds wherein R<sub>1</sub> denotes a hydrogen atom or a prodrug group have valuable pharmacological properties, pharmaceutical compositions containing the  
15 pharmacologically active compounds, the use thereof and processes for preparing them.

In the above general formula I

20 X denotes an oxygen or sulphur atom,

R<sub>1</sub> denotes a hydrogen atom or a prodrug group such as a C<sub>1-4</sub>-alkoxycarbonyl or C<sub>2-4</sub>-alkanoyl group,

25 R<sub>2</sub> denotes a carboxy group, a straight-chain or branched C<sub>1-6</sub>-alkoxy-carbonyl group, a C<sub>4-7</sub>-cycloalkoxy-carbonyl or an aryloxycarbonyl group,

a straight-chain or branched C<sub>1-6</sub>-alkoxy-carbonyl group, which is terminally substituted in the alkyl moiety by a phenyl, heteroaryl, carboxy, C<sub>1-3</sub>-alkoxy-carbonyl, aminocarbonyl,  
30 C<sub>1-3</sub>-alkylamino-carbonyl or di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl group,



a straight-chain or branched C<sub>2-6</sub>-alkoxy-carbonyl group, which is terminally substituted in the alkyl moiety by a chlorine atom or a hydroxy, C<sub>1-3</sub>-alkoxy, amino, C<sub>1-3</sub>-alkylamino or di-(C<sub>1-3</sub>-alkyl)-amino group,

5 an aminocarbonyl or methylaminocarbonyl group, an ethylaminocarbonyl group optionally substituted in the 2 position of the ethyl group by a hydroxy or C<sub>1-3</sub>-alkoxy group or, if R<sub>4</sub> does not denote an aminosulphonyl-phenyl or N-(C<sub>1-5</sub>-alkyl)-C<sub>1-3</sub>-alkylaminocarbonyl-phenyl group, it may also denote a di-(C<sub>1-2</sub>-alkyl)-aminocarbonyl group,

10 R<sub>3</sub> denotes a hydrogen atom, a C<sub>1-6</sub>-alkyl, C<sub>3-7</sub>-cycloalkyl, trifluoromethyl or heteroaryl group,

a phenyl or naphthyl group, a phenyl or naphthyl group mono- or disubstituted by a fluorine, chlorine, bromine or iodine atom, by a trifluoromethyl, C<sub>1-3</sub>-alkyl or C<sub>1-3</sub>-alkoxy group, whilst in the event of disubstitution the substituents may be identical or different and wherein the abovementioned unsubstituted as well as the mono- and disubstituted phenyl and naphthyl groups may additionally be substituted

by a hydroxy, hydroxy-C<sub>1-3</sub>-alkyl or C<sub>1-3</sub>-alkoxy-C<sub>1-3</sub>-alkyl group,

by a cyano, carboxy, carboxy-C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-3</sub>-alkylamino-carbonyl or di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl group,

by a nitro group,

by an amino, C<sub>1-3</sub>-alkylamino, di-(C<sub>1-3</sub>-alkyl)-amino or amino-C<sub>1-3</sub>-alkyl group,

by a C<sub>1-3</sub>-alkylcarbonylamino, N-(C<sub>1-3</sub>-alkyl)-C<sub>1-3</sub>-alkyl-carbonylamino, C<sub>1-3</sub>-alkylcarbonylamino-C<sub>1-3</sub>-alkyl, N-(C<sub>1-3</sub>-alkyl)-C<sub>1-3</sub>-alkylcarbonylamino-C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkyl-sulphonylamino,

C<sub>1-3</sub>-alkylsulphonylamino-C<sub>1-3</sub>-alkyl, N-(C<sub>1-3</sub>-alkyl)-  
C<sub>1-3</sub>-alkylsulphonylamino-C<sub>1-3</sub>-alkyl or aryl-C<sub>1-3</sub>-alkylsulphonylamino group,

by a cycloalkylamino, cycloalkyleneimino, cycloalkyleneiminocarbonyl,  
cycloalkyleneimino-C<sub>1-3</sub>-alkyl, cycloalkyleneiminocarbonyl-C<sub>1-3</sub>-alkyl or  
cycloalkyleneiminosulphonyl-C<sub>1-3</sub>-alkyl group having 4 to 7 ring members in each  
case, whilst in each case the methylene group in position 4 of a 6- or 7-membered  
cycloalkyleneimino group may be replaced by an oxygen or sulphur atom, by a  
sulphinyl, sulphonyl, -NH or -N(C<sub>1-3</sub>-alkyl) group,

or by a heteroaryl or heteroaryl-C<sub>1-3</sub>-alkyl group,

R<sub>4</sub> denotes a C<sub>3-7</sub>-cycloalkyl group,

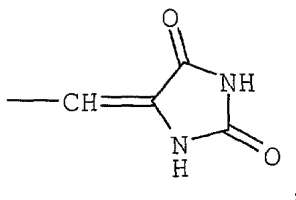
whilst the methylene group in the 4 position of a 6- or 7-membered cycloalkyl group  
may be substituted by an amino, C<sub>1-3</sub>-alkylamino or di-(C<sub>1-3</sub>-alkyl)-amino group or  
replaced by an -NH or -N(C<sub>1-3</sub>-alkyl) group,

or a phenyl group substituted by the group R<sub>6</sub>, which may additionally be mono- or  
disubstituted by fluorine, chlorine, bromine or iodine atoms, by C<sub>1-5</sub>-alkyl, trifluoromethyl,  
hydroxy, C<sub>1-3</sub>-alkoxy, carboxy, C<sub>1-3</sub>-alkoxycarbonyl, amino, acetylamino,  
C<sub>1-3</sub>-alkyl-sulphonylamino, aminocarbonyl, C<sub>1-3</sub>-alkyl-aminocarbonyl, di-(C<sub>1-3</sub>-al-  
kyl)-aminocarbonyl, aminosulphonyl, C<sub>1-3</sub>-alkyl-aminosulphonyl,  
di-(C<sub>1-3</sub>-alkyl)-aminosulphonyl, nitro or cyano groups, wherein the substituents may be  
identical or different and wherein

R<sub>6</sub> denotes a hydrogen, fluorine, chlorine, bromine or iodine atom,

a cyano, nitro, amino, C<sub>1-5</sub>-alkyl, C<sub>3-7</sub>-cycloalkyl, trifluoromethyl, phenyl, tetrazolyl or  
heteroaryl group,

the group of formula



wherein the hydrogen atoms bound to a nitrogen atom may in each case be replaced independently of one another by a C<sub>1-3</sub>-alkyl group,

a C<sub>1-3</sub>-alkoxy group, a C<sub>1-3</sub>-alkoxy-C<sub>1-3</sub>-alkoxy, phenyl-C<sub>1-3</sub>-alkoxy, amino-C<sub>2-3</sub>-alkoxy, C<sub>1-3</sub>-alkylamino-C<sub>2-3</sub>-alkoxy, di-(C<sub>1-3</sub>-alkyl)-amino-C<sub>2-3</sub>-alkoxy, phenyl-C<sub>1-3</sub>-alkylamino-C<sub>2-3</sub>-alkoxy, N-(C<sub>1-3</sub>-alkyl)-phenyl-C<sub>1-3</sub>-alkylamino-C<sub>2-3</sub>-alkoxy, C<sub>5-7</sub>-cycloalkyleneimino-C<sub>2-3</sub>-alkoxy or C<sub>1-3</sub>-alkylmercapto group,

a carboxy, C<sub>1-4</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-3</sub>-alkylamino-carbonyl, N-(C<sub>1-5</sub>-alkyl)-C<sub>1-3</sub>-alkylaminocarbonyl, phenyl-C<sub>1-3</sub>-alkylamino-carbonyl, N-(C<sub>1-3</sub>-alkyl)-phenyl-C<sub>1-3</sub>-alkylamino-carbonyl, piperazinocarbonyl or N-(C<sub>1-3</sub>-alkyl)-piperazinocarbonyl group,

a C<sub>1-3</sub>-alkylaminocarbonyl or N-(C<sub>1-5</sub>-alkyl)-C<sub>1-3</sub>-alkylaminocarbonyl group wherein an alkyl moiety is substituted by a carboxy or C<sub>1-3</sub>-alkoxycarbonyl group or in the 2 or 3 position by a di-(C<sub>1-3</sub>-alkyl)-amino, piperazino, N-(C<sub>1-3</sub>-alkyl)-piperazino or a 4- to 7-membered cycloalkyleneimino group,

a C<sub>3-7</sub>-cycloalkyl-carbonyl group,

wherein the methylene group in the 4 position of the 6- or 7-membered cycloalkyl moiety may be substituted by an amino, C<sub>1-3</sub>-alkylamino or di-(C<sub>1-3</sub>-alkyl)-amino group or replaced by an -NH or -N(C<sub>1-3</sub>-alkyl) group,

a 4- to 7-membered cycloalkyleneimino group wherein

a methylene group linked to the imino group may be replaced by a carbonyl or sulphonyl group or

the cycloalkylene moiety may be fused to a phenyl ring or

one or two hydrogen atoms may each be replaced by a C<sub>1-3</sub>-alkyl group and/or

in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be substituted by a carboxy, C<sub>1-3</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-3</sub>-alkylaminocarbonyl, di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl, phenyl-C<sub>1-3</sub>-alkylamino or N-(C<sub>1-3</sub>-alkyl)-phenyl-C<sub>1-3</sub>-alkylamino group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH, -N(C<sub>1-3</sub>-alkyl), -N(phenyl), -N(C<sub>1-3</sub>-alkyl-carbonyl) or -N(benzoyl) group,

a C<sub>1-4</sub>-alkyl group substituted by the group R<sub>7</sub>, wherein

R<sub>7</sub> denotes a C<sub>3-7</sub>-cycloalkyl group,

whilst the methylene group in the 4 position of a 6- or 7-membered cycloalkyl group may be substituted by an amino, C<sub>1-3</sub>-alkylamino or di-(C<sub>1-3</sub>-alkyl)-amino group or replaced by an -NH or -N(C<sub>1-3</sub>-alkyl) group or

in a 5- to 7-membered cycloalkyl group a -(CH<sub>2</sub>)<sub>2</sub> group may be replaced by a -CO-NH group, a -(CH<sub>2</sub>)<sub>3</sub> group may be replaced by a -NH-CO-NH or -CO-NH-CO group or a -(CH<sub>2</sub>)<sub>4</sub> group may be replaced by a -NH-CO-NH-CO group, whilst in each case a hydrogen atom bound to a nitrogen atom may be replaced by a C<sub>1-3</sub>-alkyl group,

an aryl or heteroaryl group,

a hydroxy or C<sub>1-3</sub>-alkoxy group,

an amino, C<sub>1-7</sub>-alkylamino, di-(C<sub>1-7</sub>-alkyl)-amino, phenylamino,  
N-phenyl-C<sub>1-3</sub>-alkyl-amino, phenyl-C<sub>1-3</sub>-alkylamino, N-(C<sub>1-3</sub>-alkyl)-phenyl-  
C<sub>1-3</sub>-alkylamino or di-(phenyl-C<sub>1-3</sub>-alkyl)-amino group,

an ω-hydroxy-C<sub>2-3</sub>-alkyl-amino, N-(C<sub>1-3</sub>-alkyl)-ω-hydroxy-C<sub>2-3</sub>-alkyl-amino,  
di-(ω-hydroxy-C<sub>2-3</sub>-alkyl)-amino, di-(ω-(C<sub>1-3</sub>-alkoxy)-C<sub>2-3</sub>-alkyl)-amino or N-(dioxo-  
lan-2-yl)-C<sub>1-3</sub>-alkyl-amino group,

a C<sub>1-3</sub>-alkylcarbonylamino-C<sub>2-3</sub>-alkyl-amino or  
C<sub>1-3</sub>-alkylcarbonylamino-C<sub>2-3</sub>-alkyl-N-(C<sub>1-3</sub>-alkyl)-amino group,

a C<sub>1-3</sub>-alkylsulphonylamino, N-(C<sub>1-3</sub>-alkyl)-C<sub>1-3</sub>-alkylsulphonylamino,  
C<sub>1-3</sub>-alkylsulphonylamino-C<sub>2-3</sub>-alkyl-amino or  
C<sub>1-3</sub>-alkylsulphonylamino-C<sub>2-3</sub>-alkyl-N-(C<sub>1-3</sub>-alkyl)-amino group,

a hydroxycarbonyl-C<sub>1-3</sub>-alkylamino or N-(C<sub>1-3</sub>-alkyl)-  
hydroxycarbonyl-C<sub>1-3</sub>-alkyl-amino group,

a guanidino group wherein one or two hydrogen atoms may each be replaced by a C<sub>1-3</sub>-alkyl group,

a group of formula



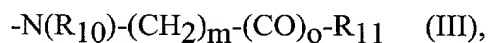
wherein

R<sub>8</sub> denotes a hydrogen atom or a C<sub>1-3</sub>-alkyl group,

n denotes one of the numbers 0, 1, 2 or 3 and

R<sub>9</sub> denotes an amino, C<sub>1-4</sub>-alkylamino, di-(C<sub>1-4</sub>-alkyl)-amino, phenylamino, N-(C<sub>1-4</sub>-alkyl)-phenylamino, benzylamino, N-(C<sub>1-4</sub>-alkyl)-benzylamino or C<sub>1-4</sub>-alkoxy group, a 4- to 7-membered cycloalkyleneimino group, whilst in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH, -N(C<sub>1-3</sub>-alkyl), -N(phenyl), -N(C<sub>1-3</sub>-alkyl-carbonyl) or -N(benzoyl) group, or, if n denotes one of the numbers 1, 2 or 3, it may also denote a hydrogen atom,

a group of formula



wherein

R<sub>10</sub> denotes a hydrogen atom, a C<sub>1-3</sub>-alkyl group, a C<sub>1-3</sub>-alkylcarbonyl, arylcarbonyl, phenyl-C<sub>1-3</sub>-alkyl-carbonyl, C<sub>1-3</sub>-alkylsulphonyl, arylsulphonyl or phenyl-C<sub>1-3</sub>-alkylsulphonyl group,

m denotes one of the numbers 1, 2, 3 or 4,

o denotes the number 1 or, if m denotes one of the numbers 2, 3 or 4, o may also denote the number 0 and

R<sub>11</sub> denotes an amino, C<sub>1-4</sub>-alkylamino, di-(C<sub>1-4</sub>-alkyl)-amino, phenylamino, N-(C<sub>1-4</sub>-alkyl)-phenylamino, benzylamino, N-(C<sub>1-4</sub>-alkyl)-benzylamino, C<sub>1-4</sub>-alkoxy or C<sub>1-3</sub>-alkoxy-C<sub>1-3</sub>-alkoxy group, a di-(C<sub>1-4</sub>-alkyl)-amino-C<sub>1-3</sub>-alkylamino group optionally substituted in the 1 position by a C<sub>1-3</sub>-alkyl group or a 4- to 7-membered cycloalkyleneimino group, wherein the cycloalkylene

moiety may be fused to a phenyl ring or in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH, -N(C<sub>1-3</sub>-alkyl), -N(phenyl), -N(C<sub>1-3</sub>-alkyl-carbonyl) or -N(benzoyl) group,

5

a C<sub>4-7</sub>-cycloalkylamino, C<sub>4-7</sub>-cycloalkyl-C<sub>1-3</sub>-alkylamino or C<sub>4-7</sub>-cycloalkenylamino group wherein position 1 of the ring is not involved in the double bond and wherein the abovementioned groups may each additionally be substituted at the amino-nitrogen atom by a C<sub>5-7</sub>-cycloalkyl, C<sub>2-4</sub>-alkenyl or C<sub>1-4</sub>-alkyl group,

10

a 4- to 7-membered cycloalkyleneimino group, wherein

the cycloalkylene moiety may be fused to a phenyl group or to an oxazolo, imidazolo, thiazolo, pyridino, pyrazino or pyrimidino group optionally substituted by a fluorine, chlorine, bromine or iodine atom, by a nitro, C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkoxy or amino group, and/or

15

one or two hydrogen atoms may each be replaced by a C<sub>1-3</sub>-alkyl, C<sub>5-7</sub>-cycloalkyl or phenyl group and/or

20

the methylene group in the 3 position of a 5-membered cycloalkyleneimino group may be substituted by a hydroxy, hydroxy-C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkoxy or C<sub>1-3</sub>-alkoxy-C<sub>1-3</sub>-alkyl group,

25

the methylene group in the 3 or 4 position of a 6- or 7-membered cycloalkyleneimino group may in each case be substituted by a hydroxy, hydroxy-C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkoxy, C<sub>1-3</sub>-alkoxy-C<sub>1-3</sub>-alkyl, carboxy, C<sub>1-4</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-3</sub>-alkylaminocarbonyl, di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl, phenyl-C<sub>1-3</sub>-alkylamino or N-(C<sub>1-3</sub>-alkyl)-phenyl-C<sub>1-3</sub>-alkyl-amino group or

30

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH,  
 -N(C<sub>1-3</sub>-alkyl-), -N(phenyl), -N(phenyl-C<sub>1-3</sub>-alkyl-), -N(C<sub>1-3</sub>-alkyl-carbonyl-),  
 -N(C<sub>1-4</sub>-hydroxy-carbonyl-), -N(C<sub>1-4</sub>-alkoxy-carbonyl-), -N(benzoyl-) or  
 -N(phenyl-C<sub>1-3</sub>-alkyl-carbonyl-) group,

5

wherein a methylene group linked to an imino-nitrogen atom of the  
 cycloalkyleneimino group may be replaced by a carbonyl or sulphonyl  
 group or in a 5- to 7-membered monocyclic cycloalkyleneimino group or a  
 cycloalkyleneimino group fused to a phenyl group the two methylene  
 groups linked to the imino-nitrogen atom may each be replaced by a  
 carbonyl group,

10

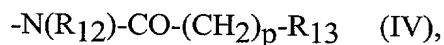
or R<sub>6</sub> denotes a C<sub>1-4</sub>-alkyl group which is substituted by a carboxy, C<sub>1-3</sub>-alkoxycarbonyl,  
 aminocarbonyl, C<sub>1-3</sub>-alkylaminocarbonyl or di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl group or by a 4-  
 to 7-membered cycloalkyleneiminocarbonyl group,

15

an N-(C<sub>1-3</sub>-alkyl)-C<sub>2-4</sub>-alkanoylamino group which is additionally substituted in the alkyl  
 moiety by a carboxy or C<sub>1-3</sub>-alkoxycarbonyl group,

20

a group of formula



25 wherein

R<sub>12</sub> denotes a hydrogen atom, a C<sub>1-6</sub>-alkyl or C<sub>3-7</sub>-cycloalkyl group or a C<sub>1-3</sub>-alkyl  
 group terminally substituted by a phenyl, heteroaryl, trifluoromethyl, hydroxy,  
 C<sub>1-3</sub>-alkoxy, aminocarbonyl, C<sub>1-4</sub>-alkylamino-carbonyl, di-(C<sub>1-4</sub>-alkyl)-  
 amino-carbonyl, C<sub>1-3</sub>-alkyl-carbonyl, C<sub>1-3</sub>-alkyl-sulphonylamino,

30



N-(C<sub>1-3</sub>-alkyl)-C<sub>1-3</sub>-alkyl-sulphonylamino, C<sub>1-3</sub>-alkyl-aminosulphonyl or di-(C<sub>1-3</sub>-alkyl)-aminosulphonyl group and

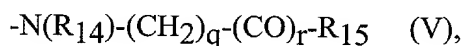
p denotes one of the numbers 0, 1, 2 or 3 and

5

R<sub>13</sub> assumes the meanings of the abovementioned group R<sub>7</sub>, or, if p denotes one of the numbers 1, 2 or 3, it may also denote a hydrogen atom,

a group of formula

10



wherein

15

R<sub>14</sub> denotes a hydrogen atom, a C<sub>1-4</sub>-alkyl group, a C<sub>1-3</sub>-alkylcarbonyl, arylcarbonyl, phenyl-C<sub>1-3</sub>-alkylcarbonyl, heteroarylcarbonyl, heteroaryl-C<sub>1-3</sub>-alkylcarbonyl, C<sub>1-4</sub>-alkylsulphonyl, arylsulphonyl, phenyl-C<sub>1-3</sub>-alkylsulphonyl, heteroarylsulphonyl or heteroaryl-C<sub>1-3</sub>-alkyl-sulphonyl group,

20

q denotes one of the numbers 1, 2, 3 or 4,

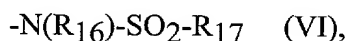
r denotes the number 1 or, if q is one of the numbers 2, 3 or 4, it may also denote the number 0 and

25

R<sub>15</sub> assumes the meanings of the abovementioned group R<sub>7</sub>,

a group of formula

30



wherein

R<sub>16</sub> denotes a hydrogen atom or a C<sub>1-4</sub>-alkyl group optionally terminally substituted by a cyano, trifluoromethyl-carbonylamino or N-(C<sub>1-3</sub>-alkyl)-trifluoromethyl-carbonyl-amino group and

R<sub>17</sub> denotes a C<sub>1-3</sub>-alkyl group,

an amino group substituted by a di-(C<sub>1-3</sub>-alkyl)-amino-C<sub>1-3</sub>-alkyl-carbonyl or di-(C<sub>1-3</sub>-alkyl)-amino-C<sub>1-3</sub>-alkyl-sulphonyl group and a di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl-C<sub>1-3</sub>-alkyl group,

or an N-(C<sub>1-3</sub>-alkyl)-C<sub>1-5</sub>-alkylsulphonylamino or N-(C<sub>1-3</sub>-alkyl)-phenylsulphonylamino group wherein the alkyl moiety is additionally substituted by a cyano or carboxy group,

wherein all the single-bonded or fused phenyl groups contained in the groups mentioned under R<sub>6</sub> may be mono- or disubstituted by fluorine, chlorine, bromine or iodine atoms, by C<sub>1-5</sub>-alkyl, trifluoromethyl, hydroxy, C<sub>1-3</sub>-alkoxy, carboxy, C<sub>1-3</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-4</sub>-alkylamino-carbonyl, di-(C<sub>1-4</sub>-alkyl)-amino-carbonyl, aminosulphonyl, C<sub>1-3</sub>-alkyl-aminosulphonyl, di-(C<sub>1-3</sub>-alkyl)-aminosulphonyl, C<sub>1-3</sub>-alkyl-sulphonylamino, nitro or cyano groups, wherein the substituents may be identical or different, or two adjacent hydrogen atoms of the phenyl groups may be replaced by a methylenedioxy group,

and

R<sub>5</sub> denotes a hydrogen atom or a C<sub>1-3</sub>-alkyl group,

wherein by an aryl group is meant a phenyl or naphthyl group optionally mono- or disubstituted by a fluorine, chlorine, bromine or iodine atom, by a cyano, trifluoromethyl, nitro, carboxy, aminocarbonyl, C<sub>1-3</sub>-alkyl or C<sub>1-3</sub>-alkoxy group and

by a heteroaryl group is meant a monocyclic 5- or 6-membered heteroaryl group optionally substituted by a C<sub>1-3</sub>-alkyl group in the carbon skeleton, wherein

the 6-membered heteroaryl group contains one, two or three nitrogen atoms and

5

the 5-membered heteroaryl group contains an imino group optionally substituted by a C<sub>1-3</sub>-alkyl or phenyl-C<sub>1-3</sub>-alkyl group, an oxygen or sulphur atom or

an imino group optionally substituted by a C<sub>1-3</sub>-alkyl or phenyl-C<sub>1-3</sub>-alkyl group or an oxygen or sulphur atom and additionally a nitrogen atom or

10

an imino group optionally substituted by a C<sub>1-3</sub>-alkyl or phenyl-C<sub>1-3</sub>-alkyl group and two nitrogen atoms,

15

and moreover a phenyl ring may be fused to the abovementioned monocyclic heterocyclic groups via two adjacent carbon atoms and the bonding takes place via a nitrogen atom or via a carbon atom of the heterocyclic moiety or a fused phenyl ring,

some or all of the hydrogen atoms in the abovementioned alkyl and alkoxy groups or in the alkyl moieties contained in the above-defined groups of formula I optionally being replaced by fluorine atoms,

20

the saturated alkyl and alkoxy moieties with more than 2 carbon atoms which are present in the groups defined hereinbefore also include the branched isomers thereof, such as for example the isopropyl, tert.butyl, isobutyl group, unless otherwise stated, and

25

additionally the hydrogen atom of any carboxy group present or a hydrogen atom bound to a nitrogen atom, e.g. a hydrogen atom of an amino, alkylamino or imino group or a saturated N-heterocycle such as the piperidiny group, may each be replaced by a group which can be cleaved *in vivo*.

30

By a group which can be cleaved *in vivo* from an imino or amino group is meant, for example, a hydroxy group, an acyl group such as the benzoyl or pyridinoyl group or a C<sub>1-16</sub>-alkanoyl group such as the formyl, acetyl, propionyl, butanoyl, pentanoyl or hexanoyl group, an allyloxycarbonyl group, a C<sub>1-16</sub>-alkoxycarbonyl group such as the methoxy-carbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, 5 tert.butoxycarbonyl, pentoxycarbonyl, hexyloxycarbonyl, octyloxycarbonyl, nonyloxycarbonyl, decyloxycarbonyl, undecyloxycarbonyl, dodecyloxycarbonyl or hexadecyloxycarbonyl group, a phenyl-C<sub>1-6</sub>-alkoxycarbonyl group such as the benzyloxycarbonyl, phenylethoxycarbonyl or phenylpropoxycarbonyl group, a 10 C<sub>1-3</sub>-alkylsulphonyl-C<sub>2-4</sub>-alkoxycarbonyl, C<sub>1-3</sub>-alkoxy-C<sub>2-4</sub>-alkoxy-C<sub>2-4</sub>-alkoxycarbonyl or R<sub>e</sub>CO-O-(R<sub>f</sub>CR<sub>g</sub>)-O-CO group wherein

R<sub>e</sub> denotes a C<sub>1-8</sub>-alkyl, C<sub>5-7</sub>-cycloalkyl, phenyl or phenyl- C<sub>1-3</sub>-alkyl group,

15 R<sub>f</sub> denotes a hydrogen atom, a C<sub>1-3</sub>-alkyl, C<sub>5-7</sub>-cycloalkyl or phenyl group and

R<sub>g</sub> denotes a hydrogen atom, a C<sub>1-3</sub>-alkyl or R<sub>e</sub>CO-O-(R<sub>f</sub>CR<sub>g</sub>)-O group wherein R<sub>e</sub> to R<sub>g</sub> are as hereinbefore defined,

20 wherein additionally the amino group may be a phthalimido group, whilst the abovementioned ester groups may also be used as a group which can be converted *in vivo* into a carboxy group.

One sub-group of compounds of general formula I which deserves special mention comprises 25 those wherein

X, R<sub>1</sub> and R<sub>3</sub> to R<sub>5</sub> are as hereinbefore defined and

R<sub>2</sub> denotes a straight-chain or branched C<sub>1-6</sub>-alkoxy-carbonyl group, a 30 C<sub>4-7</sub>-cycloalkoxycarbonyl or a aryloxycarbonyl group,

a straight-chain or branched C<sub>1-6</sub>-alkoxy-carbonyl group, which is terminally substituted in the alkyl moiety by a phenyl, heteroaryl, carboxy, C<sub>1-3</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-3</sub>-alkylaminocarbonyl or di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl group,

- 5 a straight-chain or branched C<sub>2-6</sub>-alkoxy-carbonyl group, which is terminally substituted in the alkyl moiety by a chlorine atom or a hydroxy, C<sub>1-3</sub>-alkoxy, amino, C<sub>1-3</sub>-alkylamino or di-(C<sub>1-3</sub>-alkyl)-amino group,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts  
10 thereof.

A second sub-group of compounds of general formula I which deserves special mention comprises those wherein

- 15 X, R<sub>1</sub> and R<sub>3</sub> to R<sub>5</sub> are as hereinbefore defined and

R<sub>2</sub> denotes an aminocarbonyl or methylaminocarbonyl group, an ethylaminocarbonyl group optionally substituted in the 2 position of the ethyl group by a hydroxy or C<sub>1-3</sub>-alkoxy group or, if R<sub>4</sub> does not denote an aminosulphonyl-phenyl or N-(C<sub>1-5</sub>-alkyl)-  
20 C<sub>1-3</sub>-alkylaminocarbonyl-phenyl group, R<sub>2</sub> may also denote a di-(C<sub>1-2</sub>-alkyl)-aminocarbonyl group,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts  
25 thereof.

A third sub-group of compounds of general formula I which deserves special mention comprises those wherein

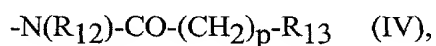
X, R<sub>1</sub> to R<sub>3</sub> and R<sub>5</sub> are as hereinbefore defined and

30 R<sub>4</sub> denotes an R<sub>7</sub>-(C<sub>1-4</sub>-alkyl)-phenyl group, wherein

R<sub>7</sub> denotes an amino, C<sub>1-7</sub>-alkylamino, di-(C<sub>1-7</sub>-alkyl)-amino, phenylamino, N-phenyl-C<sub>1-3</sub>-alkyl-amino, phenyl-C<sub>1-3</sub>-alkylamino, N-(C<sub>1-3</sub>-alkyl)-phenyl-C<sub>1-3</sub>-alkylamino or di-(phenyl-C<sub>1-3</sub>-alkyl)-amino group,

5

or a phenyl group substituted by the group of formula



10

wherein R<sub>12</sub>, p and R<sub>13</sub> are as hereinbefore defined,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

15

Preferred compounds of general formula I are those wherein

R<sub>1</sub> and R<sub>3</sub> are as hereinbefore defined and

20

X denotes an oxygen atom,

R<sub>2</sub> denotes a carboxy group, a straight-chain or branched C<sub>1-6</sub>-alkoxy-carbonyl group, a C<sub>5-7</sub>-cycloalkoxycarbonyl or a phenoxycarbonyl group,

25

a straight-chain or branched C<sub>1-3</sub>-alkoxy-carbonyl group, which is terminally substituted in the alkyl moiety by a phenyl, heteroaryl, carboxy, C<sub>1-3</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-3</sub>-alkylaminocarbonyl or di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl group,

30

a straight-chain or branched C<sub>2-3</sub>-alkoxy-carbonyl group, which is terminally substituted in the alkyl moiety by a chlorine atom, by a hydroxy, C<sub>1-3</sub>-alkoxy, amino, C<sub>1-3</sub>-alkylamino or di-(C<sub>1-3</sub>-alkyl)-amino group,

an aminocarbonyl or methylaminocarbonyl group, an ethylaminocarbonyl group optionally substituted in the 2 position of the ethyl group by a hydroxy or C<sub>1-3</sub>-alkoxy group or, if R<sub>4</sub> does not denote an aminosulphonyl-phenyl or N-(C<sub>1-5</sub>-alkyl)-C<sub>1-3</sub>-alkylaminocarbonyl-phenyl group, it may also denote a di-(C<sub>1-2</sub>-alkyl)-aminocarbonyl group,

R<sub>4</sub> denotes a C<sub>3-7</sub>-cycloalkyl group,

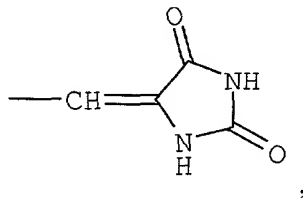
whilst the methylene group in the 4 position of a 6- or 7-membered cycloalkyl group may be substituted by an amino, C<sub>1-3</sub>-alkylamino or di-(C<sub>1-3</sub>-alkyl)-amino group or replaced by an -NH or -N(C<sub>1-3</sub>-alkyl) group,

or a phenyl group substituted by the group R<sub>6</sub>, which may additionally be mono- or disubstituted by fluorine, chlorine or bromine atoms, by C<sub>1-3</sub>-alkyl, trifluoromethyl, hydroxy, C<sub>1-3</sub>-alkoxy, carboxy, C<sub>1-3</sub>-alkoxycarbonyl, amino, acetylamino, aminocarbonyl, C<sub>1-3</sub>-alkyl-aminocarbonyl, di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl, nitro or cyano groups, wherein the substituents may be identical or different and wherein

R<sub>6</sub> denotes a hydrogen, fluorine, chlorine, bromine or iodine atom,

a cyano, nitro, amino, C<sub>1-5</sub>-alkyl, C<sub>3-7</sub>-cycloalkyl, trifluoromethyl, phenyl, tetrazolyl or heteroaryl group,

the group of formula



wherein a hydrogen atom bound to the nitrogen atom may be replaced by a C<sub>1-3</sub>-alkyl group,

a C<sub>1-3</sub>-alkoxy group, an amino-C<sub>2-3</sub>-alkoxy, C<sub>1-3</sub>-alkylamino-C<sub>2-3</sub>-alkoxy, di-(C<sub>1-3</sub>-alkyl)-amino-C<sub>2-3</sub>-alkoxy, phenyl-C<sub>1-3</sub>-alkylamino-C<sub>2-3</sub>-alkoxy, N-(C<sub>1-3</sub>-alkyl)-phenyl-C<sub>1-3</sub>-alkylamino-C<sub>2-3</sub>-alkoxy, pyrrolidino-C<sub>2-3</sub>-alkoxy, piperidino-C<sub>2-3</sub>-alkoxy or C<sub>1-3</sub>-alkylmercapto group,

5

a carboxy, C<sub>1-4</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-3</sub>-alkylamino-carbonyl, phenyl-C<sub>1-3</sub>-alkylamino-carbonyl or N-(C<sub>1-3</sub>-alkyl)-phenyl-C<sub>1-3</sub>-alkylamino-carbonyl group,

10 a C<sub>3-7</sub>-cycloalkyl-carbonyl group,

wherein the methylene group in the 4 position of the 6- or 7-membered cycloalkyl moiety may be replaced by an -NH or -N(C<sub>1-3</sub>-alkyl) group,

15 a 4- to 7-membered cycloalkyleneimino group, wherein

a methylene group linked to the imino group may be replaced by a carbonyl or sulphonyl group or

20 one or two hydrogen atoms may each be replaced by a C<sub>1-3</sub>-alkyl group and/or

in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be substituted by a carboxy, C<sub>1-3</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-3</sub>-alkylaminocarbonyl, di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl, phenyl-C<sub>1-3</sub>-alkylamino or N-(C<sub>1-3</sub>-alkyl)-phenyl-C<sub>1-3</sub>-alkylamino group or

25

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH or -N(C<sub>1-3</sub>-alkyl) group,

30 a C<sub>1-4</sub>-alkyl group terminally substituted by the group R<sub>7</sub>, wherein



R<sub>7</sub> denotes a C<sub>5-7</sub>-cycloalkyl group,

whilst the methylene group in the 4 position of a 6- or 7-membered cycloalkyl group may be replaced by an -NH or -N(C<sub>1-3</sub>-alkyl) group or

5

in a 5- to 7-membered cycloalkyl group a -(CH<sub>2</sub>)<sub>2</sub> group may be replaced by a -CO-NH group, a -(CH<sub>2</sub>)<sub>3</sub> group may be replaced by a -NH-CO-NH- or a -(CH<sub>2</sub>)<sub>4</sub> group may be replaced by a -NH-CO-NH-CO group, whilst in each case a hydrogen atom bound to a nitrogen atom may be replaced by a C<sub>1-3</sub>-alkyl group,

10

a phenyl or heteroaryl group,

a hydroxy or C<sub>1-3</sub>-alkoxy group,

15

an amino, C<sub>1-6</sub>-alkylamino, di-(C<sub>1-6</sub>-alkyl)-amino, phenylamino, N-phenyl-C<sub>1-3</sub>-alkyl-amino, phenyl-C<sub>1-3</sub>-alkylamino, N-(C<sub>1-3</sub>-alkyl)-phenyl-C<sub>1-3</sub>-alkylamino or di-(phenyl-C<sub>1-3</sub>-alkyl)-amino group,

20

a ω-hydroxy-C<sub>2-3</sub>-alkyl-amino, N-(C<sub>1-3</sub>-alkyl)-ω-hydroxy--C<sub>2-3</sub>-alkyl-amino, di-(ω-hydroxy-C<sub>2-3</sub>-alkyl)-amino, di-(ω-(C<sub>1-3</sub>-alkoxy)-C<sub>2-3</sub>-alkyl)-amino or N-(dioxolan-2-yl)-C<sub>1-3</sub>-alkyl-amino group,

a C<sub>1-3</sub>-alkylcarbonylamino-C<sub>2-3</sub>-alkyl-amino or

25

C<sub>1-3</sub>-alkylcarbonylamino-C<sub>2-3</sub>-alkyl-N-(C<sub>1-3</sub>-alkyl)-amino group,

a C<sub>1-3</sub>-alkylsulphonylamino, N-(C<sub>1-3</sub>-alkyl)-C<sub>1-3</sub>-alkylsulphonylamino,

C<sub>1-3</sub>-alkylsulphonylamino--C<sub>2-3</sub>-alkyl-amino or C<sub>1-3</sub>-alkylsulphonylamino-C<sub>2-3</sub>-alkyl-N-(C<sub>1-3</sub>-alkyl)-amino group,

30

a hydroxycarbonyl-C<sub>1-3</sub>-alkylamino or

N-(C<sub>1-3</sub>-alkyl)-hydroxycarbonyl-C<sub>1-3</sub>-alkyl-amino group

a guanidino group wherein a hydrogen atom may be replaced by a C<sub>1-3</sub>-alkyl group,

5

a group of formula



10

wherein

R<sub>8</sub> denotes a hydrogen atom or a C<sub>1-3</sub>-alkyl group,

n denotes one of the numbers 0, 1, 2 or 3 and

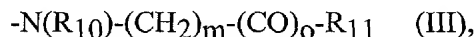
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R<sub>9</sub> denotes an amino, C<sub>1-3</sub>-alkylamino, di-(C<sub>1-3</sub>-alkyl)-amino, phenylamino, benzylamino or C<sub>1-4</sub>-alkoxy group, a 5- to 7-membered cycloalkyleneimino group, wherein the methylene group in position 4 of the piperidino group may be replaced by an oxygen or sulphur atom, by an -NH, -N(C<sub>1-3</sub>-alkyl), -N(phenyl), -N(C<sub>1-3</sub>-alkyl-carbonyl) or -N(benzoyl) group, or, if n denotes one of the numbers 1, 2 or 3, it may also denote a hydrogen atom,

20

a group of formula

25



wherein

R<sub>10</sub> denotes a hydrogen atom, a C<sub>1-3</sub>-alkyl group, a C<sub>1-3</sub>-alkylcarbonyl or C<sub>1-3</sub>-alkylsulphonyl group,

30

m denotes one of the numbers 1, 2 or 3,

o denotes the number 1 or, if m is one of the numbers 2 or 3, o may also denote the number 0 and

5

R<sub>11</sub> denotes an amino, C<sub>1-3</sub>-alkylamino, di-(C<sub>1-3</sub>-alkyl)-amino, C<sub>1-4</sub>-alkoxy or C<sub>1-3</sub>-alkoxy-C<sub>1-3</sub>-alkoxy group or a 5- to 7-membered cycloalkyleneimino group, wherein the methylene group in position 4 of the piperidino group may be replaced by an oxygen or sulphur atom, by an -NH, -N(C<sub>1-3</sub>-alkyl), -N(phenyl),  
10 -N(C<sub>1-3</sub>-alkyl-carbonyl) or -N(benzoyl) group,

a C<sub>4-7</sub>-cycloalkylamino or C<sub>4-7</sub>-cycloalkenylamino group wherein position 1 of the ring is not involved in the double bond,

15

a 4- to 7-membered cycloalkyleneimino group, wherein

the cycloalkylene moiety may be fused to a phenyl group or

one or two hydrogen atoms may each be replaced by a C<sub>1-3</sub>-alkyl group and/or

20

the methylene group in position 3 of the pyrrolidino group may be substituted by a hydroxy or C<sub>1-3</sub>-alkoxy group,

25

in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be substituted by a hydroxy, hydroxy-C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkoxy, carboxy, C<sub>1-3</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-3</sub>-alkylamino-carbonyl, di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl, phenyl-C<sub>1-3</sub>-alkylamino or N-(C<sub>1-3</sub>-alkyl)-phenyl-C<sub>1-3</sub>-alkylamino group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH, -N(C<sub>1-3</sub>-alkyl), -N(phenyl), -N(phenyl-C<sub>1-3</sub>-alkyl), -N(C<sub>1-3</sub>-alkyl-carbonyl), -N(C<sub>1-4</sub>-alkoxy-carbonyl), -N(benzoyl) or -N(phenyl-C<sub>1-3</sub>-alkyl-carbonyl) group,

5 wherein a methylene group linked to an imino-nitrogen atom of the cycloalkyleneimino group may be replaced by a carbonyl or sulphonyl group or in a 5- to 6-membered monocyclic cycloalkyleneimino group or a cycloalkyleneimino group fused to a phenyl group the two methylene groups linked to the imino-nitrogen atom may each be replaced by a  
10 carbonyl group,

or R<sub>6</sub> denotes a C<sub>1-4</sub>-alkyl group which is terminally substituted by a carboxy, C<sub>1-3</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-3</sub>-alkylaminocarbonyl or  
15 di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl group or by a 4- to 7-membered cycloalkyleneiminocarbonyl group,

a group of formula

20 
$$-N(R_{12})-CO-(CH_2)_p-R_{13} \quad (IV),$$

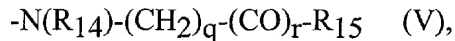
wherein

R<sub>12</sub> denotes a hydrogen atom, a C<sub>1-3</sub>-alkyl, C<sub>5-7</sub>-cycloalkyl, phenyl-C<sub>1-3</sub>-alkyl or  
25 heteroaryl-C<sub>1-3</sub>-alkyl group and

p denotes one of the numbers 0, 1, 2 or 3 and

R<sub>13</sub> assumes the meanings of the abovementioned group R<sub>7</sub>, or, if p denotes one of  
30 the numbers 1, 2 or 3, it may also denote a hydrogen atom,

a group of formula



5 wherein

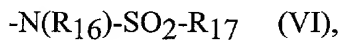
$\text{R}_{14}$  denotes a hydrogen atom, a  $\text{C}_{1-4}$ -alkyl group, a  $\text{C}_{1-3}$ -alkylcarbonyl, phenylcarbonyl, phenyl- $\text{C}_{1-3}$ -alkylcarbonyl, heteroarylcarbonyl, heteroaryl- $\text{C}_{1-3}$ -alkylcarbonyl,  $\text{C}_{1-4}$ -alkylsulphonyl, phenylsulphonyl, phenyl- $\text{C}_{1-3}$ -alkylsulphonyl- heteroarylsulphonyl or heteroaryl- $\text{C}_{1-3}$ -alkyl-sulphonyl group,

$q$  denotes one of the numbers 1, 2, 3 or 4,

15  $r$  denotes the number 1 or, if  $q$  is one of the numbers 2, 3 or 4, it may also denote the number 0 and

$\text{R}_{15}$  assumes the meanings of the abovementioned group  $\text{R}_7$ ,

20 a group of formula



wherein

25  $\text{R}_{16}$  denotes a hydrogen atom or a  $\text{C}_{1-4}$ -alkyl group optionally terminally substituted by a cyano, trifluoromethyl-carbonylamino or  $\text{N}-(\text{C}_{1-3}\text{-alkyl})$ -trifluoromethyl-carbonyl-amino group and

$\text{R}_{17}$  denotes a  $\text{C}_{1-3}$ -alkyl group,

30

an amino group substituted by a di-(C<sub>1-3</sub>-alkyl)-amino-C<sub>1-3</sub>-alkyl-carbonyl or di-(C<sub>1-3</sub>-alkyl)-amino-C<sub>1-3</sub>-alkyl-sulphonyl group and a di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl-C<sub>1-3</sub>-alkyl group,

5            wherein all the single-bonded or fused phenyl groups contained in the groups mentioned under R<sub>6</sub> may be mono- or disubstituted by fluorine, chlorine or bromine atoms, by C<sub>1-3</sub>-alkyl, trifluoromethyl, hydroxy, C<sub>1-3</sub>-alkoxy, carboxy, C<sub>1-3</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-3</sub>-alkyl-aminocarbonyl, aminosulphonyl, C<sub>1-3</sub>-alkyl-aminosulphonyl, nitro or cyano groups, wherein the  
10            substituents may be identical or different, or two adjacent hydrogen atoms of the phenyl groups may be replaced by a methylenedioxy group, and

R<sub>5</sub> denotes a hydrogen atom or a C<sub>1-3</sub>-alkyl group,

15            whilst by a heteroaryl group as mentioned above is meant a pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, furyl, thienyl, oxazolyl, thiazolyl, pyrazolyl, imidazolyl or triazolyl group optionally substituted in the carbon skeleton by a C<sub>1-3</sub>-alkyl group wherein a hydrogen atom bound to a nitrogen atom may be replaced by a C<sub>1-3</sub>-alkyl or phenyl-C<sub>1-3</sub>-alkyl group and wherein the 5-membered heteroaryl groups containing at least  
20            one imino group are bound via a carbon or nitrogen atom,

a hydrogen atom bound to a nitrogen atom in the abovementioned groups may be replaced by a group which can be cleaved *in vivo*, particularly by an acetyl or tert.butoxycarbonyl group,

25            the carboxy groups contained in the abovementioned groups may each be substituted by a group which can be cleaved *in vivo* and may occur, for example, in the form of the tert.butoxycarbonyl group,

some or all of the hydrogen atoms in the abovementioned alkyl and alkoxy groups or in the alkyl moieties contained in the above-defined groups of formula I optionally being replaced by fluorine atoms and

- 5 the saturated alkyl and alkoxy moieties contained in the abovementioned groups, which contain more than 2 carbon atoms, may be straight-chain or branched, unless otherwise stated,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts  
10 thereof.

One subgroup of preferred compounds of general formula I deserving special mention comprises those wherein

- 15 X, R<sub>1</sub> and R<sub>3</sub> to R<sub>5</sub> are as hereinbefore defined and

R<sub>2</sub> denotes a straight-chain or branched C<sub>1-6</sub>-alkoxy-carbonyl group, a C<sub>5-7</sub>-cycloalkoxycarbonyl or a phenoxycarbonyl group,

- 20 a straight-chain or branched C<sub>1-3</sub>-alkoxy-carbonyl group, which is terminally substituted in the alkyl moiety by a phenyl- carboxy, C<sub>1-3</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-3</sub>-alkylaminocarbonyl or di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl group,

- a straight-chain or branched C<sub>2-3</sub>-alkoxy-carbonyl group, which is terminally substituted in  
25 the alkyl moiety by a hydroxy, C<sub>1-3</sub>-alkoxy, amino, C<sub>1-3</sub>-alkylamino or di-(C<sub>1-3</sub>-alkyl)-amino group,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

30

A second sub-group of preferred compounds of general formula I deserving special mention comprises those wherein

X, R<sub>1</sub> and R<sub>3</sub> to R<sub>5</sub> are as hereinbefore defined and

5

R<sub>2</sub> denotes an aminocarbonyl or methylaminocarbonyl group, an ethylaminocarbonyl group optionally substituted in the 2 position of the ethyl group by a hydroxy or C<sub>1-3</sub>-alkoxy group or, if R<sub>4</sub> does not denote an aminosulphonyl-phenyl or N-(C<sub>1-5</sub>-alkyl)-C<sub>1-3</sub>-alkylaminocarbonyl-phenyl group, R<sub>2</sub> may also denote a di-(C<sub>1-2</sub>-alkyl)-aminocarbonyl group,

10

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

15

A third sub-group of preferred compounds of general formula I deserving special mention comprises those wherein

X, R<sub>1</sub> to R<sub>3</sub> and R<sub>5</sub> are as hereinbefore defined and

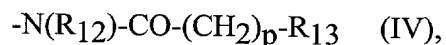
20

R<sub>4</sub> denotes an R<sub>7</sub>-(n-C<sub>1-4</sub>-alkyl)-phenyl group, wherein

R<sub>7</sub> denotes an amino, C<sub>1-6</sub>-alkylamino, di-(C<sub>1-6</sub>-alkyl)-amino, phenylamino, N-phenyl-C<sub>1-3</sub>-alkyl-amino, phenyl-C<sub>1-3</sub>-alkylamino, N-(C<sub>1-3</sub>-alkyl)-phenyl-C<sub>1-3</sub>-alkylamino or di-(phenyl-C<sub>1-3</sub>-alkyl)-amino group,

25

or a phenyl group substituted by the group of formula



30

wherein R<sub>12</sub>, p and R<sub>13</sub> are as hereinbefore defined,



the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

5 Particularly preferred compounds of general formula I are those wherein

X denotes an oxygen atom,

R<sub>1</sub> denotes a hydrogen atom,

10

R<sub>2</sub> denotes a carboxy group, a straight-chain or branched C<sub>1-4</sub>-alkoxycarbonyl group or a phenoxycarbonyl group,

15

a straight-chain or branched C<sub>1-3</sub>-alkoxy-carbonyl group, which is terminally substituted in the alkyl moiety by a phenyl, carboxy, C<sub>1-3</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-3</sub>-alkylaminocarbonyl or di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl group,

20

a straight-chain or branched C<sub>2-3</sub>-alkoxy-carbonyl group which is terminally substituted in the alkyl moiety by a hydroxy, C<sub>1-3</sub>-alkoxy, amino, C<sub>1-3</sub>-alkylamino or di-(C<sub>1-3</sub>-alkyl)-amino group,

25

an aminocarbonyl or methylaminocarbonyl group, an ethylaminocarbonyl group optionally substituted in the 2 position of the ethyl group by a hydroxy or C<sub>1-3</sub>-alkoxy group or, if R<sub>4</sub> does not denote an aminosulphonyl-phenyl or N-(C<sub>1-5</sub>-alkyl)-C<sub>1-3</sub>-alkylaminocarbonyl-phenyl group, it may also denote a di-(C<sub>1-2</sub>-alkyl)-aminocarbonyl group,

30

R<sub>3</sub> denotes a C<sub>1-4</sub>-alkyl group or a phenyl group which may be substituted by a fluorine, chlorine or bromine atom, by a trifluoromethyl, C<sub>1-3</sub>-alkyl, hydroxy or C<sub>1-3</sub>-alkoxy group,

R<sub>4</sub> denotes a C<sub>5-6</sub>-cycloalkyl group,

wherein the methylene group in position 4 of the cyclohexyl group may be substituted by an amino, C<sub>1-3</sub>-alkylamino or di-(C<sub>1-3</sub>-alkyl)-amino group or replaced by an -NH or -N(C<sub>1-3</sub>-alkyl) group,

5

a phenyl group, a phenyl group disubstituted by C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkoxy or nitro groups, wherein the substituents may be identical or different, or

10

a phenyl group substituted by the group R<sub>6</sub>, which may additionally be substituted by a fluorine, chlorine or bromine atom or by an amino or nitro group, wherein R<sub>6</sub> denotes a fluorine, chlorine or bromine atom,

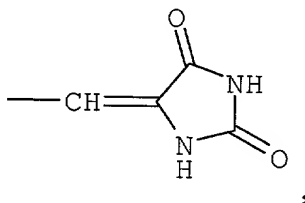
a C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkoxy, nitro, amino or C<sub>5-6</sub>-cycloalkyl group,

15

a pyrrolyl, pyrazolyl, imidazolyl, triazolyl or tetrazolyl group bound via a carbon atom, wherein the abovementioned heteroaromatic groups in the carbon skeleton may be substituted by a C<sub>1-3</sub>-alkyl group or a hydrogen atom bound to a nitrogen atom may be replaced by a C<sub>1-3</sub>-alkyl or phenyl-C<sub>1-3</sub>-alkyl group,

20

the group of formula



a carboxy, C<sub>1-4</sub>-alkoxycarbonyl, phenyl-C<sub>1-3</sub>-alkylamino-carbonyl or C<sub>5-7</sub>-cycloalkyl-carbonyl group,

25

a 5 or 6-membered cycloalkyleneimino group, wherein

the methylene group in position 4 of the piperidino group may be replaced by an oxygen or sulphur atom, by an -NH or -N(C<sub>1-3</sub>-alkyl) group,

an unbranched C<sub>1-3</sub>-alkyl group terminally substituted by the group R<sub>7</sub>, wherein

5

R<sub>7</sub> denotes a C<sub>5-7</sub>-cycloalkyl group,

10

wherein in a 5 or 6-membered cycloalkyl group a -(CH<sub>2</sub>)<sub>2</sub> group may be replaced by a -CO-NH group, a -(CH<sub>2</sub>)<sub>3</sub> group may be replaced by an -NH-CO-NH- or a -(CH<sub>2</sub>)<sub>4</sub> group may be replaced by an -NH-CO-NH-CO group, whilst in each case a hydrogen atom bound to a nitrogen atom may be replaced by a C<sub>1-3</sub>-alkyl group,

15

a phenyl or pyridinyl group or a pyrrolyl, pyrazolyl, imidazolyl or triazolyl group bound via a carbon or nitrogen atom, wherein the abovementioned heteroaromatic groups in the carbon skeleton may be substituted by a C<sub>1-3</sub>-alkyl group or a hydrogen atom bound to a nitrogen atom may be replaced by a C<sub>1-3</sub>-alkyl group,

20

a hydroxy or C<sub>1-3</sub>-alkoxy group,

an amino, C<sub>1-6</sub>-alkylamino, di-(C<sub>1-6</sub>-alkyl)-amino, phenylamino, N-phenyl-C<sub>1-3</sub>-alkylamino, phenyl-C<sub>1-3</sub>-alkylamino or N-(C<sub>1-3</sub>-alkyl)-phenyl-C<sub>1-3</sub>-alkylamino group,

25

a ω-hydroxy-C<sub>2-3</sub>-alkyl-amino, N-(C<sub>1-3</sub>-alkyl)-ω-hydroxy-C<sub>2-3</sub>-alkylamino, di-(ω-hydroxy-C<sub>2-3</sub>-alkyl)-amino or di-(ω-(C<sub>1-3</sub>-alkoxy)-C<sub>2-3</sub>-alkyl)-amino group,

a C<sub>1-3</sub>-alkylcarbonylamino-C<sub>2-3</sub>-alkyl-amino or C<sub>1-3</sub>-alkylcarbonylamino-C<sub>2-3</sub>-alkyl-N-(C<sub>1-3</sub>-alkyl)-amino group,

30

a C<sub>1-3</sub>-alkylsulphonylamino, N-(C<sub>1-3</sub>-alkyl)-C<sub>1-3</sub>-alkylsulphonylamino,  
C<sub>1-3</sub>-alkylsulphonylamino--C<sub>2-3</sub>-alkylamino or C<sub>1-3</sub>-alkylsulphonylamino-  
-C<sub>2-3</sub>-alkyl-N-(C<sub>1-3</sub>-alkyl)-amino group,

5 a hydroxycarbonyl-C<sub>1-3</sub>-alkylamino or  
N-(C<sub>1-3</sub>-alkyl)-hydroxycarbonyl-C<sub>1-3</sub>-alkyl-amino group,

a guanidino group wherein a hydrogen atom may be replaced by a C<sub>1-3</sub>-alkyl group,

10 a group of formula



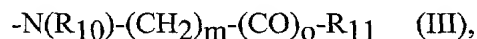
wherein

15 R<sub>8</sub> denotes a hydrogen atom or a C<sub>1-3</sub>-alkyl group,

n denotes one of the numbers 0, 1, 2 or 3 and

20 R<sub>9</sub> denotes an amino, C<sub>1-3</sub>-alkylamino, di-(C<sub>1-3</sub>-alkyl)-amino or C<sub>1-4</sub>-alkoxy  
group, a 5- or 6-membered cycloalkyleneimino group, wherein the methylene  
group in position 4 of the piperidino group may be replaced by an -NH,  
-N(C<sub>1-3</sub>-alkyl) or -N(C<sub>1-3</sub>-alkyl-carbonyl) group, or, if n denotes one of the  
numbers 1, 2 or 3, R<sub>9</sub> may also denote a hydrogen atom,

25 a group of formula



30 wherein

$R_{10}$  denotes a hydrogen atom or a  $C_{1-3}$ -alkyl group,

m denotes one of the numbers 1, 2 or 3,

5 o denotes the number 1 or, if m is one of the numbers 2 or 3, o may also denote the number 0 and

$R_{11}$  denotes an amino,  $C_{1-3}$ -alkylamino, di- $(C_{1-3}$ -alkyl)-amino,  $C_{1-4}$ -alkoxy or methoxy- $C_{1-3}$ -alkoxy group or a 5- or 6-membered cycloalkyleneimino group,  
10 wherein the methylene group in position 4 of the piperidino group may be replaced by an -NH, -N( $C_{1-3}$ -alkyl) or -N( $C_{1-3}$ -alkyl-carbonyl) group,

an azetidino, pyrrolidino, piperidino, 2,6-dimethyl-piperidino,  
3,5-dimethyl-piperidino or azepino group, wherein

15 the methylene group in position 3 of the pyrrolidino group may be substituted by a hydroxy group,

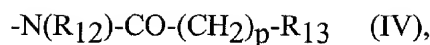
the methylene group in position 4 of the piperidino group may be substituted by  
20 a hydroxy, hydroxy- $C_{1-3}$ -alkyl or  $C_{1-3}$ -alkoxy group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH,  
-N( $C_{1-3}$ -alkyl), -N( $C_{1-3}$ -alkyl-carbonyl), -N(benzoyl) or -N(phenyl- $C_{1-3}$ -alkyl-  
carbonyl) group,

25 wherein a methylene group linked to an imino-nitrogen atom of the pyrrolidino, piperidino or piperazino group may be replaced by a carbonyl group,

30 or  $R_6$  denotes a straight-chain  $C_{1-3}$ -alkyl group which is terminally substituted by a carboxy or  $C_{1-3}$ -alkoxy-carbonyl group,

a group of formula



5

wherein

$R_{12}$  denotes a hydrogen atom, a  $C_{1-3}$ -alkyl or phenyl- $C_{1-3}$ -alkyl group,

10

$p$  denotes one of the numbers 0, 1 or 2 and

$R_{13}$  denotes an amino,  $C_{1-4}$ -alkylamino, di- $(C_{1-4}$ -alkyl)-amino, benzylamino, N- $(C_{1-3}$ -alkyl)-benzylamino,  $C_{1-3}$ -alkoxy- $C_{1-3}$ -alkylamino, N- $(C_{1-3}$ -alkyl)- $C_{1-3}$ -alkoxy- $C_{1-3}$ -alkylamino, di-(2-methoxy-ethyl)-amino, di-( $\omega$ -hydroxy- $C_{2-3}$ -alkyl)-amino or aminocarbonyl-methyl-N-(methyl)-amino group,

15

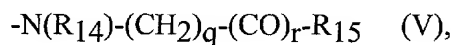
a pyrrolyl, pyrazolyl or imidazolyl group bound via a nitrogen atom and optionally substituted by a  $C_{1-3}$ -alkyl group,

20

a pyrrolidino, piperidino, morpholino, thiomorpholino or a piperazino group optionally substituted in the 4 position by a  $C_{1-3}$ -alkyl, phenyl- $C_{1-3}$ -alkyl,  $C_{1-3}$ -alkylcarbonyl or  $C_{1-4}$ -alkoxycarbonyl group or, if  $n$  denotes the number 1 or 2, it may also denote a hydrogen atom,

25

a group of formula



wherein

30

R<sub>14</sub> denotes a hydrogen atom, a C<sub>1-4</sub>-alkyl, C<sub>1-3</sub>-alkyl-carbonyl, phenylcarbonyl, phenyl-C<sub>1-3</sub>-alkylcarbonyl, furyl-carbonyl, pyridinyl-carbonyl, furyl-C<sub>1-3</sub>-alkyl-carbonyl, pyridinyl-C<sub>1-3</sub>-alkylcarbonyl, C<sub>1-4</sub>-alkylsulphonyl, phenylsulphonyl or phenyl-C<sub>1-3</sub>-alkylsulphonyl group,

5

q denotes one of the numbers 1, 2 or 3,

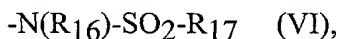
r denotes the number 1 or, if q is one of the numbers 2 or 3, it may also denote the number 0 and

10

R<sub>15</sub> denotes an amino, C<sub>1-4</sub>-alkylamino, di-(C<sub>1-4</sub>-alkyl)-amino, phenylamino, N-(C<sub>1-4</sub>-alkyl)-phenylamino, benzylamino or N-(C<sub>1-4</sub>-alkyl)-benzylamino group,

or a group of formula

15



wherein

R<sub>16</sub> denotes a hydrogen atom or a C<sub>1-3</sub>-alkyl group optionally terminally substituted by a cyano, trifluoromethyl-carbonylamino or N-(C<sub>1-3</sub>-alkyl)-trifluoromethyl-carbonyl-amino group and

20

R<sub>17</sub> denotes a C<sub>1-3</sub>-alkyl group,

25

wherein all the single-bonded or fused phenyl groups contained in the groups mentioned under R<sub>6</sub> may be substituted by a fluorine, chlorine or bromine atom, by a methyl, trifluoromethyl, methoxy, nitro or cyano group and

R<sub>5</sub> denotes a hydrogen atom,

30

wherein a hydrogen atom bound to a nitrogen atom in the abovementioned groups may be replaced by an acetyl or tert.butoxycarbonyl group,

the carboxy groups contained in the abovementioned groups may also be present in the  
5 form of the tert.butoxycarbonyl precursor group and

the saturated alkyl and alkoxy moieties contained in the abovementioned groups, which contain more than 2 carbon atoms, may be straight-chain or branched, unless otherwise stated,

10

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

One subgroup of particularly preferred compounds of general formula I deserving special  
15 mention comprises those wherein

X, R<sub>1</sub>, R<sub>3</sub> and R<sub>5</sub> are as hereinbefore defined,

R<sub>2</sub> denotes a straight-chain or branched C<sub>1-4</sub>-alkoxycarbonyl group or a phenoxycarbonyl  
20 group,

a straight-chain or branched C<sub>1-3</sub>-alkoxycarbonyl group, which is terminally substituted in the alkyl moiety by a phenyl- carboxy, C<sub>1-3</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-3</sub>-alkylaminocarbonyl or di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl group, or

25

a straight-chain or branched C<sub>2-3</sub>-alkoxy-carbonyl group, which is terminally substituted in the alkyl moiety by a hydroxy, C<sub>1-3</sub>-alkoxy, amino, C<sub>1-3</sub>-alkylamino or di-(C<sub>1-3</sub>-alkyl)-amino group, and

30 R<sub>4</sub> denotes an R<sub>7</sub>-(n-C<sub>1-3</sub>-alkyl)-phenyl group, wherein



R<sub>7</sub> denotes an amino, C<sub>1-6</sub>-alkylamino, di-(C<sub>1-4</sub>-alkyl)-amino,  
 ω-hydroxy-C<sub>2-3</sub>-alkyl-amino, N-(C<sub>1-3</sub>-alkyl)-ω-hydroxy-C<sub>2-3</sub>-alkyl-amino,  
 di-(ω-hydroxy-C<sub>2-3</sub>-alkyl)-amino or di-(ω-(C<sub>1-3</sub>-alkoxy)-C<sub>2-3</sub>-alkyl)-amino group,

5 or a phenyl group substituted by the group of formula



wherein R<sub>12</sub>, p and R<sub>13</sub> are as hereinbefore defined,

10

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

15

A second subgroup of particularly preferred compounds of general formula I deserving special mention comprises those wherein

X, R<sub>1</sub>, R<sub>3</sub> and R<sub>5</sub> are as hereinbefore defined,

20

R<sub>2</sub> denotes an aminocarbonyl or methylaminocarbonyl group, an ethylaminocarbonyl group optionally substituted in the 2 position of the ethyl group by a hydroxy or C<sub>1-3</sub>-alkoxy group or, if R<sub>4</sub> does not denote an aminosulphonyl-phenyl or N-(C<sub>1-5</sub>-alkyl)-C<sub>1-3</sub>-alkylaminocarbonyl-phenyl group, R<sub>2</sub> may also denote a di-(C<sub>1-2</sub>-alkyl)-aminocarbonyl group and

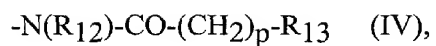
25

R<sub>4</sub> denotes a R<sub>7</sub>-(n-C<sub>1-3</sub>-alkyl)-phenyl group, wherein

30

R<sub>7</sub> denotes an amino, C<sub>1-6</sub>-alkylamino, di-(C<sub>1-4</sub>-alkyl)-amino,  
 ω-hydroxy-C<sub>2-3</sub>-alkyl-amino, N-(C<sub>1-3</sub>-alkyl)-ω-hydroxy-C<sub>2-3</sub>-alkyl-amino,  
 di-(ω-hydroxy-C<sub>2-3</sub>-alkyl)-amino or di-(ω-(C<sub>1-3</sub>-alkoxy)-C<sub>2-3</sub>-alkyl)-amino group,

or a phenyl group substituted by the group of formula



wherein  $R_{12}$ ,  $p$  and  $R_{13}$  are as hereinbefore defined,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

Most particularly preferred compounds of general formula I are those wherein

X denotes an oxygen atom,

$R_1$  and  $R_5$  each denote a hydrogen atom,

$R_2$  denotes a methoxycarbonyl, ethoxycarbonyl or aminocarbonyl group,

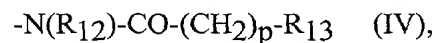
$R_3$  denotes a phenyl group and

$R_4$  denotes a phenyl group monosubstituted by the group  $R_6$ , wherein

$R_6$  denotes an N-methyl-imidazol-2-yl group,

an unbranched  $C_{1-3}$ -alkyl group which is terminally substituted by a  $C_{1-4}$ -alkylamino, di- $(C_{1-4}$ -alkyl)-amino, piperidino or 2,6-dimethyl-piperidino group,

a group of formula



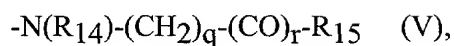
wherein

R<sub>12</sub> denotes a C<sub>1-3</sub>-alkyl group,

p denotes one of the numbers 1 or 2 and

5 R<sub>13</sub> denotes a di-(C<sub>1-3</sub>-alkyl)-amino group,

or a group of formula



10

wherein

R<sub>14</sub> denotes a C<sub>1-3</sub>-alkyl-carbonyl or C<sub>1-3</sub>-alkylsulphonyl group,

15 q denotes one of the numbers 1, 2 or 3,

r denotes the number 1 or, if q is one of the numbers 2 or 3, r may also denote the number 0 and

20 R<sub>15</sub> denotes a di-(C<sub>1-3</sub>-alkyl)-amino group,

wherein the saturated alkyl moieties contained in the abovementioned groups which contain more than 2 carbon atoms may be straight-chain or branched, unless otherwise stated,

25

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

30

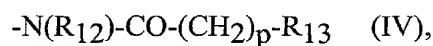
A subgroup of most particularly preferred compounds of general formula I deserving special mention comprises those wherein

X, R<sub>1</sub>, R<sub>3</sub> and R<sub>5</sub> are as hereinbefore defined,

R<sub>2</sub> denotes a methoxycarbonyl or ethoxycarbonyl group and

5 R<sub>4</sub> denotes a di-(C<sub>1-3</sub>-alkyl)-amino-C<sub>1-3</sub>-alkylphenyl group or

a phenyl group substituted by the group of formula



10

wherein R<sub>12</sub>, p and R<sub>13</sub> are as hereinbefore defined,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

15

The following are mentioned as examples of particularly preferred compounds:

(a) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

20

(b) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone,

(c) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

25

(d) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

30

(e) 3-Z-[1-(4-((2,6-dimethyl-piperidin-1-yl)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

(f) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

5 (g) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

(h) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

10

(i) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(j) 3-Z-[1-(4-(N-acetyl-N-dimethylaminocarbonylmethyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

15

(k) 3-Z-[1-(4-ethylaminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

20 (l) 3-Z-[1-(4-(1-methyl-imidazol-2-yl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(m) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

25

(n) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(o) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

30

(p) 3-Z-[1-(4-(N-dimethylaminocarbonylmethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(q) 3-Z-[1-(4-(N-((2-dimethylamino-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(r) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone and

(s) 3-Z-[1-(4-methylaminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

the tautomers, the mixtures and the salts thereof.

Another subgroup of compounds of general formula I comprises those wherein X denotes an oxygen or sulphur atom,

R<sub>1</sub> denotes a hydrogen atom or a prodrug group such as a C<sub>1-4</sub>-alkoxycarbonyl or C<sub>2-4</sub>-alkanoyl group,

R<sub>2</sub> denotes a carboxy group, a straight-chain or branched C<sub>1-6</sub>-alkoxycarbonyl group, a C<sub>5-7</sub>-cycloalkoxycarbonyl or phenyl-C<sub>1-3</sub>-alkoxycarbonyl group, an aminocarbonyl or C<sub>1-2</sub>-alkylaminocarbonyl group or, if R<sub>4</sub> does not denote an aminosulphonyl-phenyl or N-(C<sub>1-5</sub>-alkyl)-C<sub>1-3</sub>-alkylaminocarbonyl-phenyl group, a di-(C<sub>1-2</sub>-alkyl)-aminocarbonyl group,

R<sub>3</sub> denotes a hydrogen atom, a C<sub>1-6</sub>-alkyl, C<sub>3-7</sub>-cycloalkyl, trifluoromethyl or heteroaryl group,

a phenyl or naphthyl group, a phenyl or naphthyl group mono- or disubstituted by a fluorine, chlorine, bromine or iodine atom, by a trifluoromethyl, C<sub>1-3</sub>-alkyl or C<sub>1-3</sub>-alkoxy

group, whilst in the event of disubstitution the substituents may be identical or different and wherein the abovementioned unsubstituted as well as the mono- and disubstituted phenyl and naphthyl groups may additionally be substituted

5 by a hydroxy, hydroxy-C<sub>1-3</sub>-alkyl or C<sub>1-3</sub>-alkoxy-C<sub>1-3</sub>-alkyl group,

by a cyano, carboxy, carboxy-C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-3</sub>-alkylamino-carbonyl or di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl group,

10 by a nitro group,

by an amino, C<sub>1-3</sub>-alkylamino, di-(C<sub>1-3</sub>-alkyl)-amino or amino-C<sub>1-3</sub>-alkyl group,

15 by a C<sub>1-3</sub>-alkylcarbonylamino, N-(C<sub>1-3</sub>-alkyl)-C<sub>1-3</sub>-alkyl-carbonylamino, C<sub>1-3</sub>-alkylcarbonylamino-C<sub>1-3</sub>-alkyl, N-(C<sub>1-3</sub>-alkyl)-C<sub>1-3</sub>-alkylcarbonylamino-C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkyl-sulphonylamino, C<sub>1-3</sub>-alkylsulphonylamino-C<sub>1-3</sub>-alkyl, N-(C<sub>1-3</sub>-alkyl)-C<sub>1-3</sub>-alkylsulphonylamino-C<sub>1-3</sub>-alkyl or aryl-C<sub>1-3</sub>-alkylsulphonylamino group,

20 by a cycloalkylamino, cycloalkyleneimino, cycloalkyleneiminocarbonyl, cycloalkyleneimino-C<sub>1-3</sub>-alkyl, cycloalkyleneiminocarbonyl-C<sub>1-3</sub>-alkyl or cycloalkyleneiminosulphonyl-C<sub>1-3</sub>-alkyl group having 4 to 7 ring members in each case, whilst in each case the methylene group in position 4 of a 6- or 7-membered cycloalkyleneimino group may be replaced by an oxygen or sulphur atom, by a  
25 sulphinyl, sulphonyl, -NH or -N(C<sub>1-3</sub>-alkyl) group,

or by a heteroaryl or heteroaryl-C<sub>1-3</sub>-alkyl group,

R<sub>4</sub> denotes a C<sub>3-7</sub>-cycloalkyl group,

30

whilst the methylene group in the 4 position of a 6- or 7-membered cycloalkyl group may be substituted by an amino, C<sub>1-3</sub>-alkylamino or di-(C<sub>1-3</sub>-alkyl)-amino group or replaced by an -NH or -N(C<sub>1-3</sub>-alkyl) group,

- 5 or a phenyl group substituted by the group R<sub>6</sub>, which may additionally be substituted by a fluorine, chlorine, bromine or iodine atom, by a C<sub>1-5</sub>-alkyl, trifluoromethyl, C<sub>1-3</sub>-alkoxy, carboxy, C<sub>1-3</sub>-alkoxycarbonyl, aminosulphonyl, nitro or cyano group, wherein

R<sub>6</sub> denotes a hydrogen, fluorine, chlorine, bromine or iodine atom,

10

a cyano, nitro, C<sub>1-5</sub>-alkyl, C<sub>3-7</sub>-cycloalkyl, trifluoromethyl, phenyl, tetrazolyl or heteroaryl group,

15

a C<sub>1-3</sub>-alkoxy group optionally substituted by 1 to 3 fluorine atoms, a C<sub>1-3</sub>-alkoxy-C<sub>1-3</sub>-alkoxy, phenyl-C<sub>1-3</sub>-alkoxy, amino-C<sub>2-3</sub>-alkoxy, C<sub>1-3</sub>-alkylamino-C<sub>2-3</sub>-alkoxy, di-(C<sub>1-3</sub>-alkyl)-amino-C<sub>2-3</sub>-alkoxy, phenyl-C<sub>1-3</sub>-alkylamino-C<sub>2-3</sub>-alkoxy, N-(C<sub>1-3</sub>-alkyl)-phenyl-C<sub>1-3</sub>-alkylamino-C<sub>2-3</sub>-alkoxy, C<sub>5-7</sub>-cycloalkyleneimino-C<sub>2-3</sub>-alkoxy or C<sub>1-3</sub>-alkylmercapto group,

20

a carboxy, C<sub>1-4</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-3</sub>-alkylamino-carbonyl, N-(C<sub>1-5</sub>-alkyl)-C<sub>1-3</sub>-alkylaminocarbonyl, phenyl-C<sub>1-3</sub>-alkylamino-carbonyl, N-(C<sub>1-3</sub>-alkyl)-phenyl-C<sub>1-3</sub>-alkylamino-carbonyl, piperazinocarbonyl or N-(C<sub>1-3</sub>-alkyl)-piperazinocarbonyl group,

25

a C<sub>1-3</sub>-alkylaminocarbonyl or N-(C<sub>1-5</sub>-alkyl)-C<sub>1-3</sub>-alkylaminocarbonyl group wherein an alkyl moiety is substituted by a carboxy or C<sub>1-3</sub>-alkoxycarbonyl group or is substituted in the 2 or 3 position by a di-(C<sub>1-3</sub>-alkyl)-amino, piperazino, N-(C<sub>1-3</sub>-alkyl)-piperazino or a 4- to 7-membered cycloalkyleneimino group,

30

a 4- to 7-membered cycloalkyleneimino group, wherein



a methylene group linked to the imino group may be replaced by a carbonyl or sulphonyl group or

the cycloalkylene moiety may be fused to a phenyl ring or

one or two hydrogen atoms may each be replaced by a C<sub>1-3</sub>-alkyl group and/or

in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be substituted by a carboxy, C<sub>1-3</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-3</sub>-alkylaminocarbonyl, di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl, phenyl-C<sub>1-3</sub>-alkylamino or N-(C<sub>1-3</sub>-alkyl)-phenyl-C<sub>1-3</sub>-alkylamino group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH, -N(C<sub>1-3</sub>-alkyl), -N(phenyl), -N(C<sub>1-3</sub>-alkyl-carbonyl) or -N(benzoyl) group,

a C<sub>1-4</sub>-alkyl group which may be substituted

by a hydroxy or C<sub>1-3</sub>-alkoxy group,

by an amino, C<sub>1-7</sub>-alkylamino, di-(C<sub>1-7</sub>-alkyl)-amino, di-N-(C<sub>1-3</sub>-alkyl)-amino-C<sub>2-3</sub>-alkylamino, tri-N,N,N'-(C<sub>1-3</sub>-alkyl)-amino-C<sub>2-3</sub>-alkylamino, phenylamino, N-phenyl-C<sub>1-3</sub>-alkyl-amino, phenyl-C<sub>1-3</sub>-alkylamino, N-(C<sub>1-3</sub>-alkyl)-phenyl-C<sub>1-3</sub>-alkylamino or di-(phenyl-C<sub>1-3</sub>-alkyl)-amino group,

by a C<sub>1-3</sub>-alkylcarbonylamino, N-(C<sub>1-3</sub>-alkyl)-C<sub>1-3</sub>-alkylcarbonylamino, C<sub>1-3</sub>-alkoxycarbonyl-C<sub>1-3</sub>-alkylamino or N-(C<sub>1-3</sub>-alkyl)-C<sub>1-3</sub>-alkoxycarbonyl-C<sub>1-3</sub>-alkylamino group,

by a C<sub>4-7</sub>-cycloalkylamino, C<sub>4-7</sub>-cycloalkyl-C<sub>1-3</sub>-alkylamino or C<sub>4-7</sub>-cycloalkenylamino group wherein position 1 of the ring is not involved in the double bond and wherein the abovementioned groups may each additionally be

substituted at the amino-nitrogen atom by a C<sub>1-3</sub>-alkyl group wherein some or all of the hydrogen atoms are replaced by fluorine atoms, by a C<sub>5-7</sub>-cycloalkyl, C<sub>2-4</sub>-alkenyl or C<sub>1-4</sub>-alkyl group,

5 by a 4- to 7-membered cycloalkyleneimino group, wherein

a methylene group linked to the imino group may be replaced by a carbonyl or sulphonyl group or

10 the cycloalkylene moiety may be fused to a phenyl group or to an oxazolo, imidazolo, thiazolo, pyridino, pyrazino or pyrimidino group optionally substituted by a fluorine, chlorine, bromine or iodine atom, by a nitro, C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkoxy or amino group or

15 one or two hydrogen atoms may each be replaced by a C<sub>1-3</sub>-alkyl, C<sub>5-7</sub>-cycloalkyl or phenyl group and/or

in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be substituted by a hydroxy, carboxy,  
20 C<sub>1-4</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-3</sub>-alkylaminocarbonyl, di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl, phenyl-C<sub>1-3</sub>-alkylamino or N-(C<sub>1-3</sub>-alkyl)-phenyl-C<sub>1-3</sub>-alkylamino group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH,  
25 -N(C<sub>1-3</sub>-alkyl), -N(phenyl), -N(C<sub>1-3</sub>-alkyl-carbonyl) or -N(benzoyl) group,

by a carboxy, C<sub>1-3</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-3</sub>-alkylaminocarbonyl or di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl group or

30 by a 4- to 7-membered cycloalkyleneiminocarbonyl group,

an amino, pyrrolidino, piperidino, morpholino, benzoylamino or N-(C<sub>1-3</sub>-alkyl)-benzoylamino group,

an N-(C<sub>1-3</sub>-alkyl)-C<sub>2-4</sub>-alkanoylamino group which is additionally substituted in the alkyl  
5 moiety by a carboxy or C<sub>1-3</sub>-alkoxycarbonyl group,

a group of formula



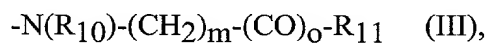
wherein

R<sub>8</sub> denotes a hydrogen atom or a C<sub>1-3</sub>-alkyl group,

n denotes one of the numbers 0, 1, 2 or 3 and

R<sub>9</sub> denotes an amino, C<sub>1-4</sub>-alkylamino, phenylamino, N-(C<sub>1-4</sub>-alkyl)-phenylamino, benzylamino, N-(C<sub>1-4</sub>-alkyl)-benzylamino or di-(C<sub>1-4</sub>-alkyl)-amino group, a 4- to 7-membered cycloalkyleneimino group, whilst in each case the methylene group in the  
4 position of a 6- or 7-membered cycloalkyleneimino group may be replaced by an  
oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH, -N(C<sub>1-3</sub>-alkyl), -N(phenyl),  
-N(C<sub>1-3</sub>-alkyl-carbonyl) or -N(benzoyl) group, or, if n denotes one of the numbers 1,  
2 or 3, it may also denote a hydrogen atom,

a group of formula



wherein

R<sub>10</sub> denotes a hydrogen atom, a C<sub>1-3</sub>-alkyl group, a C<sub>1-3</sub>-alkylcarbonyl, arylcarbonyl, phenyl-C<sub>1-3</sub>-alkylcarbonyl, C<sub>1-3</sub>-alkylsulphonyl, arylsulphonyl or phenyl-C<sub>1-3</sub>-alkylsulphonyl group,

5 m denotes one of the numbers 1, 2, 3 or 4,

o denotes one of the numbers 0 or 1 and

10 R<sub>11</sub> denotes an amino, C<sub>1-4</sub>-alkylamino, phenylamino, N-(C<sub>1-4</sub>-alkyl)-phenylamino, benzylamino, N-(C<sub>1-4</sub>-alkyl)-benzylamino or di-(C<sub>1-4</sub>-alkyl)-amino group, a 4- to 7-membered cycloalkyleneimino group, wherein the cycloalkylene moiety may be fused to a phenyl ring or in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH, -N(C<sub>1-3</sub>-alkyl), -N(phenyl),  
 15 -N(C<sub>1-3</sub>-alkyl-carbonyl) or -N(benzoyl) group, a C<sub>1-3</sub>-alkoxy group or a di-(C<sub>1-4</sub>-alkyl)-amino-C<sub>1-3</sub>-alkylamino group optionally substituted in the 1 position by a C<sub>1-3</sub>-alkyl group,

or an N-(C<sub>1-3</sub>-alkyl)-C<sub>1-5</sub>-alkylsulphonylamino or N-(C<sub>1-3</sub>-alkyl)-phenylsulphonylamino  
 20 group wherein the alkyl moiety is additionally substituted by a cyano or carboxy group,

wherein all the single-bonded or fused phenyl groups contained in the groups mentioned under R<sub>6</sub> may be mono- or disubstituted by fluorine, chlorine, bromine or iodine atoms, by C<sub>1-5</sub>-alkyl, trifluoromethyl, C<sub>1-3</sub>-alkoxy, carboxy, C<sub>1-3</sub>-alk-  
 25 oxycarbonyl, aminosulphonyl, nitro or cyano groups, wherein the substituents may be identical or different, or two adjacent hydrogen atoms of the phenyl groups may be replaced by a methylenedioxy group,

and

30

R<sub>5</sub> denotes a hydrogen atom or a C<sub>1-3</sub>-alkyl group,

wherein by an aryl group is meant a phenyl or naphthyl group optionally mono- or disubstituted by a fluorine, chlorine, bromine or iodine atom, by a trifluoromethyl, C<sub>1-3</sub>-alkyl or C<sub>1-3</sub>-alkoxy group and

5

by a heteroaryl group is meant a monocyclic 5- or 6-membered heteroaryl group optionally substituted by a C<sub>1-3</sub>-alkyl group, wherein the 6-membered heteroaryl group contains one, two or three nitrogen atoms and the 5-membered heteroaryl group contains an imino group optionally substituted by a C<sub>1-3</sub>-alkyl group, an oxygen or sulphur atom or an imino group optionally substituted by a C<sub>1-3</sub>-alkyl group and an oxygen or sulphur atom or one or two nitrogen atoms, and moreover a phenyl ring may be fused to the abovementioned monocyclic heterocyclic groups via two adjacent carbon atoms,

10

the saturated alkyl and alkoxy moieties present in the groups defined above which contain more than 2 carbon atoms also include the branched isomers thereof such as, for example, the isopropyl, tert.butyl or isobutyl group, unless otherwise stated, and

15

additionally any carboxy, amino or imino group present may be substituted by a group which can be cleaved *in vivo*,

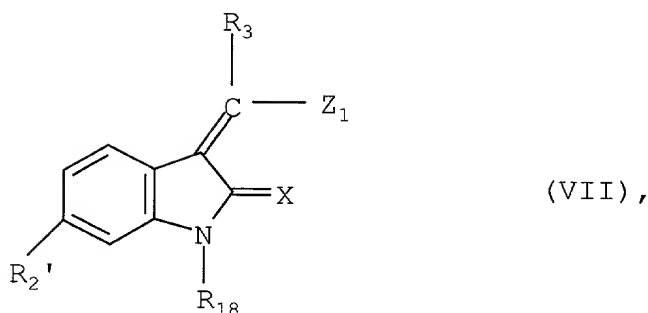
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the isomers and the salts thereof.

According to the invention the new compounds are obtained, for example, by the following methods known in principle from the literature:

25

a. reacting a compound of general formula



wherein

X and R<sub>3</sub> are as hereinbefore defined,

R<sub>2</sub>' has the meanings given for R<sub>2</sub> hereinbefore,

- 5 R<sub>18</sub> denotes a hydrogen atom or a protecting group for the nitrogen atom of the lactam group, wherein one of the groups R<sub>2</sub>' and R<sub>18</sub> may also denote a bond to a solid phase optionally formed via a spacer and the other one of the groups R<sub>2</sub>' and R<sub>18</sub> has the abovementioned meanings, and Z<sub>1</sub> denotes a halogen atom, a hydroxy, alkoxy or aryl-alkoxy group, e.g. a chlorine or bromine atom, a methoxy, ethoxy or benzyloxy group,

10 with an amine of general formula



- 15 wherein

R<sub>4</sub> and R<sub>5</sub> are as hereinbefore defined,

and if necessary subsequently cleaving any protecting group used for the nitrogen atom of the lactam group or cleaving from a solid phase.

- 20 The protecting group for the nitrogen atom of the lactam group may be, for example, an acetyl, benzoyl, ethoxycarbonyl, tert.butyloxycarbonyl or benzyloxycarbonyl group and

the solid phase may be a resin such as a 4-(2',4'-dimethoxyphenylaminomethyl)-phenoxy resin, the bond preferably being formed via the amino group, or a p-benzyloxybenzyl alcohol resin, wherein the bond is conveniently formed via an intermediate member such as a 2,5-dimethoxy-4-hydroxy-benzyl derivative.

5

The reaction is conveniently carried out in a solvent such as dimethylformamide, toluene, acetonitrile, tetrahydrofuran, dimethylsulphoxide, methylene chloride or mixtures thereof, optionally in the presence of an inert base such as triethylamine, N-ethyl-diisopropylamine or sodium hydrogen carbonate at temperatures between 20 and 175°C, whilst any

10 protecting group used can be cleaved at the same time by transamidation.

If  $Z_1$  in a compound of general formula VII denotes a halogen atom, the reaction is preferably carried out in the presence of an inert base at temperatures of between 20 and 120°C.

15

If  $Z_1$  in a compound of general formula VII denotes a hydroxy, alkoxy or arylalkoxy group, the reaction is preferably carried out at temperatures between 20 and 200°C.

20

If a protecting group used subsequently has to be cleaved, this is conveniently done either hydrolytically in an aqueous or alcoholic solvent, e.g. in methanol/water, ethanol/water, isopropanol/water, tetrahydrofuran/water, dioxan/water, dimethylformamide/water, methanol or ethanol in the presence of an alkali metal base such as lithium hydroxide, sodium hydroxide or potassium hydroxide at temperatures between 0 and 100°C, preferably at temperatures between 10 and 50°C,

25

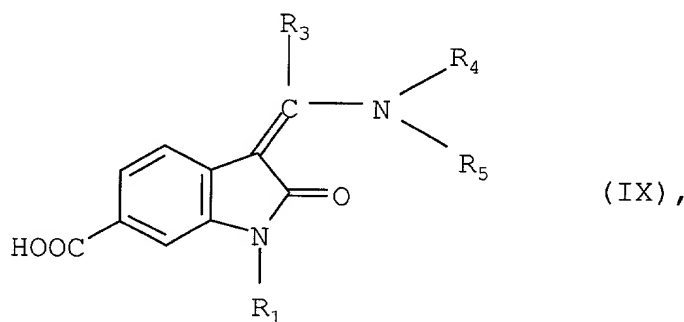
or advantageously by transamidation with an organic base such as ammonia, butylamine, dimethylamine or piperidine in a solvent such as methanol, ethanol, dimethylformamide and the mixtures thereof or in an excess of the amine used, at temperatures between 0 and 100°C, preferably at temperatures between 10 and 50°C.

30

Cleaving from any solid phase used is preferably carried out using trifluoroacetic acid and water at temperatures between 0 and 35°C, preferably at ambient temperature.

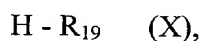
- b. In order to prepare a compound of general formula I wherein R<sub>2</sub> has the meanings given  
5 hereinbefore, with the exception of the carboxy group:

reacting a compound of general formula



wherein

R<sub>1</sub> and R<sub>3</sub> to R<sub>5</sub> are as hereinbefore defined, or the reactive derivatives thereof, with a  
compound of general formula



wherein

R<sub>19</sub> denotes a C<sub>1-6</sub>-alkanol, a C<sub>4-7</sub>-cycloalkanol or an aromatic alcohol,

- 20 a C<sub>1-6</sub>-alkanol which is terminally substituted in the alkyl moiety by a phenyl, heteroaryl, carboxy, C<sub>1-3</sub>-alkoxy-carbonyl, aminocarbonyl, C<sub>1-3</sub>-alkylamino-carbonyl or di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl group,

- a C<sub>2-6</sub>-alkanol which is terminally substituted in the alkyl moiety by a chlorine atom or a  
25 hydroxy, C<sub>1-3</sub>-alkoxy, amino, C<sub>1-3</sub>-alkylamino or di-(C<sub>1-3</sub>-alkyl)-amino group,



an amino or methylamino group, an ethylamino group optionally substituted in the 2 position of the ethyl group by a hydroxy or C<sub>1-3</sub>-alkoxy group or a di-(C<sub>1-2</sub>-alkyl)-amino group.

5

The esterification or amidation is preferably carried out in a solvent such as methylene chloride, diethylether, tetrahydrofuran, toluene, dioxan, acetonitrile, dimethylsulphoxide or dimethylformamide, optionally in the presence of an inorganic or a tertiary organic base, preferably at temperatures between 20°C and the boiling temperature of the solvent used.

- 10 The reaction with a corresponding acid is preferably carried out in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, tetraethyl orthocarbonate, trimethyl orthoacetate, 2,2-dimethoxypropane, tetramethoxysilane, thionylchloride, trimethylchlorosilane, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexyl-carbodiimide/N-hydroxysuccinimide,
- 15 N,N'-dicyclohexyl-carbodiimide/1-hydroxy-benzotriazole, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate/1-hydroxy-benzotriazole, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, and optionally with the addition of a base such as pyridine, 4-dimethylaminopyridine, N-methyl-morpholine or triethylamine,
- 20 conveniently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 100°C, and the acylation with a corresponding reactive compound such as an anhydride, ester, imidazolidine or halide thereof, is optionally carried out in the presence of a tertiary organic base such as triethylamine, N-ethyl-diisopropylamine or N-methyl-morpholine at temperatures between 0 and 150°C, preferably at temperatures between 50
- 25 and 100°C.

c. In order to prepare a compound of general formula I, wherein R<sub>4</sub> denotes a C<sub>1-4</sub>-alkyl group substituted by the group R<sub>7</sub>, wherein

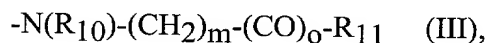
R<sub>7</sub> denotes an amino, C<sub>1-7</sub>-alkylamino, di-(C<sub>1-7</sub>-alkyl)-amino, phenylamino, N-phenyl-C<sub>1-3</sub>-alkyl-amino, phenyl-C<sub>1-3</sub>-alkylamino, N-(C<sub>1-3</sub>-alkyl)-phenyl-C<sub>1-3</sub>-alkylamino or di-(phenyl-C<sub>1-3</sub>-alkyl)-amino group,

5 a ω-hydroxy-C<sub>2-3</sub>-alkyl-amino, N-(C<sub>1-3</sub>-alkyl)-ω-hydroxy-C<sub>2-3</sub>-alkyl-amino, di-(ω-hydroxy-C<sub>2-3</sub>-alkyl)-amino, di-(ω-(C<sub>1-3</sub>-alkoxy)-C<sub>2-3</sub>-alkyl)-amino or N-(dioxolan-2-yl)-C<sub>1-3</sub>-alkyl-amino group,

10 a C<sub>1-3</sub>-alkylcarbonylamino-C<sub>2-3</sub>-alkyl-amino or C<sub>1-3</sub>-alkylcarbonylamino-C<sub>2-3</sub>-alkyl-N-(C<sub>1-3</sub>-alkyl)-amino group,

a C<sub>1-3</sub>-alkylsulphonylamino, N-(C<sub>1-3</sub>-alkyl)-C<sub>1-3</sub>-alkylsulphonylamino, C<sub>1-3</sub>-alkylsulphonylamino-C<sub>2-3</sub>-alkyl-amino or C<sub>1-3</sub>-alkylsulphonylamino-C<sub>2-3</sub>-alkyl-N-(C<sub>1-3</sub>-alkyl)-amino group,

15 a group of formula



20 wherein

R<sub>10</sub> denotes a hydrogen atom, a C<sub>1-3</sub>-alkyl group, a C<sub>1-3</sub>-alkylcarbonyl, arylcarbonyl, phenyl-C<sub>1-3</sub>-alkylcarbonyl, C<sub>1-3</sub>-alkylsulphonyl, arylsulphonyl or phenyl-C<sub>1-3</sub>-alkylsulphonyl group,

25 m denotes one of the numbers 1, 2, 3 or 4,

o denotes the number 1 and

30 R<sub>11</sub> denotes an amino, C<sub>1-4</sub>-alkylamino, di-(C<sub>1-4</sub>-alkyl)-amino, phenylamino, N-(C<sub>1-4</sub>-alkyl)-phenylamino, benzylamino, N-(C<sub>1-4</sub>-alkyl)-benzylamino,

C<sub>1-4</sub>-alkoxy or C<sub>1-3</sub>-alkoxy-C<sub>1-3</sub>-alkoxy group, a di-(C<sub>1-4</sub>-alkyl)-amino-C<sub>1-3</sub>-alkylamino group optionally substituted in the 1 position by a C<sub>1-3</sub>-alkyl group, or a 4- to 7-membered cycloalkyleneimino group, wherein the cycloalkylene moiety may be fused to a phenyl ring or in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH, -N(C<sub>1-3</sub>-alkyl), -N(phenyl), -N(C<sub>1-3</sub>-alkyl-carbonyl) or -N(benzoyl) group,

a C<sub>4-7</sub>-cycloalkylamino, C<sub>4-7</sub>-cycloalkyl-C<sub>1-3</sub>-alkylamino or C<sub>4-7</sub>-cycloalkenylamino group wherein position 1 of the ring is not involved in the double bond and wherein the abovementioned groups may each additionally be substituted at the amino-nitrogen atom by a C<sub>5-7</sub>-cycloalkyl, C<sub>2-4</sub>-alkenyl or C<sub>1-4</sub>-alkyl group,

or a 4- to 7-membered cycloalkyleneimino group, wherein

the cycloalkylene moiety may be fused to a phenyl group or to an oxazolo, imidazolo, thiazolo, pyridino, pyrazino or pyrimidino group optionally substituted by a fluorine, chlorine, bromine or iodine atom, by a nitro, C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkoxy or amino group, and/or

one or two hydrogen atoms may each be replaced by a C<sub>1-3</sub>-alkyl, C<sub>5-7</sub>-cycloalkyl or phenyl group and/or

the methylene group in the 3 position of a 5-membered cycloalkyleneimino group may be substituted by a hydroxy, hydroxy-C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkoxy or C<sub>1-3</sub>-alkoxy-C<sub>1-3</sub>-alkyl group,

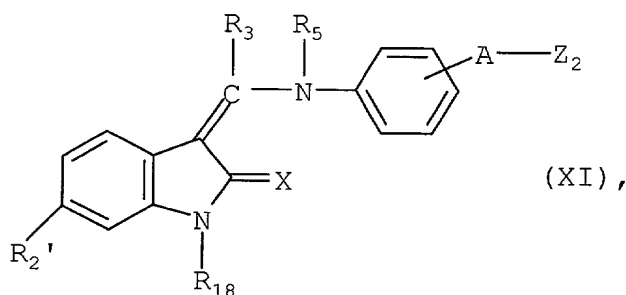
in each case the methylene group in the 3 or 4 position of a 6- or 7-membered cycloalkyleneimino group may be substituted by a hydroxy, hydroxy-C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkoxy, C<sub>1-3</sub>-alkoxy-C<sub>1-3</sub>-alkyl, C<sub>1-4</sub>-alkoxycarbonyl, aminocarbonyl,

C<sub>1-3</sub>-alkylaminocarbonyl, di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl, phenyl-C<sub>1-3</sub>-alkylamino or N-(C<sub>1-3</sub>-alkyl)-phenyl-C<sub>1-3</sub>-alkylamino group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH, -N(C<sub>1-3</sub>-alkyl-), -N(phenyl), -N(phenyl-C<sub>1-3</sub>-alkyl-), -N(C<sub>1-3</sub>-alkyl-carbonyl-), -N(C<sub>1-4</sub>-alkoxy-carbonyl-), -N(benzoyl-) or -N(phenyl-C<sub>1-3</sub>-alkyl-carbonyl-) group,

wherein a methylene group linked to an imino-nitrogen atom of the cycloalkyleneimino group may be replaced by a carbonyl or sulphonyl group or in a 5- to 7-membered monocyclic cycloalkyleneimino group or a cycloalkyleneimino group fused to a phenyl group the two methylene groups linked to the imino-nitrogen atom may each be replaced by a carbonyl group:

reacting a compound of general formula



wherein

R<sub>3</sub>, R<sub>5</sub> and X are as hereinbefore defined,

R<sub>2</sub>' has the meanings given for R<sub>2</sub> hereinbefore,

R<sub>18</sub> denotes a hydrogen atom or a protecting group for the nitrogen atom of the lactam group, wherein one of the groups R<sub>2</sub>' and R<sub>18</sub> may also denote a bond to a solid phase

optionally formed via a spacer and the other one of the groups R<sub>2</sub>' and R<sub>18</sub> has the abovementioned meanings, A denotes a C<sub>1-4</sub>-alkyl group and Z<sub>2</sub> denotes a leaving group,

for example an alkyl or arylsulphonyloxy group such as the methylsulphonyloxy, ethylsulphonyloxy, p-toluenesulphonyloxy or trifluoromethanesulphonyloxy group, with an amine of general formula

5



wherein

$\text{R}_7$  has the meanings given for  $\text{R}_7$  hereinbefore, and subsequently, if necessary, cleaving any protecting group used for the nitrogen atom of the lactam group, or cleaving from a solid phase.

The reaction is conveniently carried out in a solvent such as methylene chloride, tetrahydrofuran, 1,4-dioxan, toluene, acetonitrile, dimethylsulphoxide, dimethylformamide, dimethylacetamide, N-methylpyrrolidone or the mixtures thereof, optionally with the addition of water as a co-solvent and/or with the addition of an inert auxiliary base, e.g. sodium hydrogen carbonate, pyridine, 2,4,6-trimethylpyridine, quinoline, triethylamine, N-ethyl-diisopropylamine, N-ethyl-dicyclohexylamine, 1,4-diazabicyclo[2,2,2]octane or 1,8-diazabicyclo[5,4,0]undec-7-ene, at temperatures between  $-50^\circ\text{C}$  and  $+100^\circ\text{C}$ , preferably between  $-10^\circ\text{C}$  and  $+50^\circ\text{C}$ , while any protecting group used may be cleaved at the same time by transamidation.

If any protecting group used for the nitrogen atom of the lactam group has to be removed or if the compound has to be cleaved from a solid phase this is carried out as described under method (a) above.

If according to the invention a compound of general formula I is obtained which contains an alkoxycarbonyl group, this may be converted by hydrolysis into a corresponding carboxy compound, or

30

if a compound of general formula I is obtained which contains an amino or alkylamino group, this may be converted by reductive alkylation into a corresponding alkylamino or dialkylamino compound, or

- 5 if a compound of general formula I is obtained which contains an amino or alkylamino group, this may be converted by acylation or sulphonation into a corresponding acyl or sulphonyl compound, or

- 10 if a compound of general formula I is obtained which contains a carboxy group, this may be converted by esterification or amidation into a corresponding ester or aminocarbonyl compound, or

- 15 if a compound of general formula I is obtained which contains a cycloalkyleneimino group wherein a methylene group is replaced by a sulphur atom, this may be converted by oxidation into a corresponding sulphinyl or sulphonyl compound, or

if a compound of general formula I is obtained which contains a nitro group, this may be converted by reduction into a corresponding amino compound, or

- 20 if a compound of general formula I is obtained wherein R<sub>4</sub> denotes a phenyl group substituted by an amino, alkylamino, aminoalkyl or N-alkyl-amino group, this may subsequently be converted, by reaction with a corresponding cyanate, isocyanate or carbamoyl halide, into a corresponding urea compound of general formula I, or

- 25 if a compound of general formula I is obtained wherein R<sub>4</sub> denotes a phenyl group substituted by an amino, alkylamino, aminoalkyl or N-alkyl-amino group, this may subsequently be converted, by reaction with a corresponding compound which transfers the amidino group or by reaction with a corresponding nitrile, into a corresponding guanidino compound of general formula I.

30

The subsequent hydrolysis is preferably carried out in an aqueous solvent, e.g. in water, methanol/water, ethanol/water, isopropanol/water, tetrahydrofuran/water or dioxan/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulphuric acid or in the presence of an alkali metal base such as lithium hydroxide, sodium hydroxide or potassium hydroxide at temperatures between 0 and 100°C, preferably at temperatures between 10 and 50°C.

The subsequent reductive alkylation is preferably carried out in a suitable solvent such as methanol, methanol/water, methanol/water/ammonia, ethanol, ether, tetrahydrofuran, dioxan or dimethylformamide, optionally with the addition of an acid such as hydrochloric acid in the presence of catalytically activated hydrogen, e.g. hydrogen in the presence of Raney nickel, platinum or palladium/charcoal, or in the presence of a metal hydride such as sodium borohydride, lithium borohydride, sodium cyanoborohydride or lithium aluminium hydride at temperatures between 0 and 100°C, preferably at temperatures between 20 and 80°C.

The subsequent acylation or sulphonylation is preferably carried out with the corresponding free acid or a corresponding reactive compound such as the anhydride, ester, imidazolidine or halide thereof, preferably in a solvent such as methylene chloride, diethylether, tetrahydrofuran, toluene, dioxan, acetonitrile, dimethylsulphoxide or dimethylformamide, optionally in the presence of an inorganic or tertiary organic base at temperatures between -20 and 200°C, preferably at temperatures between 20°C and boiling temperature of the solvent used. The reaction with the free acid may optionally be carried out in the presence of an acid-activating agent or a dehydrating agent, e.g. in the presence of isobutyl chloroformate, tetraethyl orthocarbonate, trimethyl orthoacetate, 2,2-dimethoxypropane, tetramethoxysilane, thionyl chloride, trimethylchlorosilane, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-dicyclohexylcarbodiimide/1-hydroxy-benzotriazole, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate/1-hydroxy-benzotriazole, N,N'-carbonyldiimidazole

or triphenylphosphine/carbon tetrachloride, and optionally with the addition of a base such as pyridine, 4-dimethylamino-pyridine, N-methyl-morpholine or triethylamine, conveniently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 100°C. The reaction with a corresponding reactive compound may optionally be

5 carried out in the presence of a tertiary organic base such as triethylamine, N-ethyl-diisopropylamine, N-methyl-morpholine or pyridine or by using an anhydride in the presence of the corresponding acid at temperatures between 0 and 150°C, preferably at temperatures between 50 and 100°C.

10 The subsequent esterification or amidation is conveniently carried out by reacting a corresponding reactive carboxylic acid derivative with a corresponding alcohol or amine as described hereinbefore.

The subsequent oxidation of the sulphur atom is preferably carried out in a solvent or

15 mixture of solvents, e.g. in water, water/pyridine, acetone, methylene chloride, acetic acid, acetic acid/acetic anhydride, dilute sulphuric acid or trifluoroacetic acid, usefully at temperatures of between -80 and 100°C depending on the oxidising agent used.

In order to prepare a corresponding sulphonyl compound of general formula I the oxidation

20 is expediently carried out with one equivalent of the oxidising agent used, e.g. with hydrogen peroxide in glacial acetic acid, trifluoroacetic acid or formic acid at 0 to 20°C or in acetone at 0 to 60°C, with a peracid such as performic acid in glacial acetic acid or trifluoroacetic acid at 0 to 50°C or with m-chloroperbenzoic acid in methylene chloride, chloroform or dioxan at -20 to 80°C, with sodium metaperiodate in aqueous methanol or

25 ethanol at -15 to 25°C, with bromine in glacial acetic acid or aqueous acetic acid optionally in the presence of a weak base such as sodium acetate, with N-bromosuccinimide in ethanol, with tert.butyl hypochlorite in methanol at -80 to -30°C, with iodobenzodichloride in aqueous pyridine at 0 to 50°C, with nitric acid in glacial acetic acid at 0 to 20°C, with chromic acid in glacial acetic acid or in acetone at 0 to 20°C and with sulphonyl chloride in

30 methylene chloride at -70°C, the resulting thioether-chlorine complex is expediently hydrolysed with aqueous ethanol.



In order to prepare a sulphonyl compound of general formula I the oxidation is expediently carried out starting from a corresponding sulphonyl compound with one or more equivalents of the oxidising agent used or starting from a corresponding mercapto  
5 compound, expediently with two or more equivalents of the oxidising agent used, e.g. with hydrogen peroxide in glacial acetic acid/acetic anhydride, trifluoroacetic acid or in formic acid at 20 to 100°C or in acetone at 0 to 60°C, with a peracid such as performic acid or m-chloroperbenzoic acid in glacial acetic acid, trifluoroacetic acid, methylene chloride or chloroform at temperatures between 0 and 60°C, with nitric acid in glacial acetic acid at 0  
10 to 20°C, with chromic acid, sodium periodate or potassium permanganate in acetic acid, water/sulphuric acid or in acetone at 0 to 20°C.

The subsequent reduction of a nitro group is preferably carried out by hydrogenolysis, e.g. with hydrogen in the presence of a catalyst such as palladium/charcoal or Raney nickel in a  
15 solvent such as methanol, ethanol, ethyl acetate, dimethylformamide, dimethylformamide/acetone or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid or glacial acetic acid at temperatures of between 0 and 50°C, but preferably at ambient temperature, and at a hydrogen pressure of 1 to 7 bar, but preferably 3 to 5 bar.

The subsequent preparation of a corresponding urea compound of general formula I is conveniently carried out with an inorganic cyanate or a corresponding isocyanate or carbamoylchloride, preferably in a solvent such as dimethylformamide and optionally in  
20 the presence of a tertiary organic base such as triethylamine at temperatures between 0 and 50°C, preferably at ambient.

The subsequent preparation of a corresponding guanidino compound of general formula I is conveniently carried out by reacting with a compound which transfers the amidino group such as 3,5-dimethylpyrazole-1-carboxylic acid amidine, preferably in a solvent such as  
30 dimethylformamide and optionally in the presence of a tertiary organic base such as triethylamine at temperatures of between 0 and 50°C, preferably at ambient temperature.

In the reactions described hereinbefore, any reactive groups present such as carboxy, hydroxy, amino, alkylamino or imino groups may be protected during the reaction by  
5 conventional protecting groups which are cleaved again after the reaction.

For example, a protecting group for a carboxyl group may be a trimethylsilyl, methyl, ethyl, tert.butyl, benzyl or tetrahydropyranyl group and

- 10 protecting groups for a hydroxy, amino, alkylamino or imino group may be an acetyl, trifluoroacetyl, benzoyl, ethoxycarbonyl, tert.butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl or 2,4-dimethoxybenzyl group and additionally, for the amino group, a phthalyl group.
- 15 Any protecting group used is optionally subsequently cleaved for example by hydrolysis in an aqueous solvent, e.g. in water, isopropanol/water, tetrahydrofuran/water or dioxan/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulphuric acid or in the presence of an alkali metal base such as lithium hydroxide, sodium hydroxide or potassium hydroxide, at temperatures between 0 and 100°C, preferably at temperatures  
20 between 10 and 50°C.

- However, a benzyl, methoxybenzyl or benzyloxycarbonyl group is cleaved, for example, hydrogenolytically, e.g. with hydrogen in the presence of a catalyst such as palladium/charcoal in a solvent such as methanol, ethanol, ethyl acetate,  
25 dimethylformamide, dimethylformamide/acetone or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid or glacial acetic acid at temperatures between 0 and 50°C, but preferably at ambient temperature, and at a hydrogen pressure of 1 to 7 bar, but preferably 3 to 5 bar.
- 30 A methoxybenzyl group may also be cleaved in the presence of an oxidising agent such as cerium(IV)ammonium nitrate in a solvent such as methylene chloride, acetonitrile or

acetonitrile/water at temperatures of between 0 and 50°C, but preferably at ambient temperature.

5 A 2,4-dimethoxybenzyl group, however, is preferably cleaved in trifluoroacetic acid in the presence of anisole.

10 A tert.butyl or tert.butyloxycarbonyl group is preferably cleaved by treating with an acid such as trifluoroacetic acid or hydrochloric acid, optionally using a solvent such as methylene chloride, dioxan, ethyl acetate or ether.

15 A phthalyl group is preferably cleaved in the presence of hydrazine or a primary amine such as methylamine, ethylamine or n-butylamine in a solvent such as methanol, ethanol, isopropanol, toluene/water or dioxan at temperatures between 20 and 50°C.

20 Moreover, chiral compounds of general formula I obtained may be resolved into their enantiomers and/or diastereomers.

25 Thus, for example, the compounds of general formula I obtained which occur as racemates may be separated by methods known *per se* (cf. Allinger N. L. and Eliel E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes and compounds of general formula I with at least 2 asymmetric carbon atoms may be resolved into their diastereomers on the basis of their physical-chemical differences using methods known *per se*, e.g. by chromatography and/or fractional crystallisation, and, if these compounds are obtained in racemic form, they may subsequently be resolved into the enantiomers as mentioned above.

30 The enantiomers are preferably separated by column separation on chiral phases or by recrystallisation from an optically active solvent or by reacting with an optically active substance which forms salts or derivatives such as e.g. esters or amides with the racemic compound, particularly acids and the activated derivatives or alcohols thereof, and separating the mixture of diastereomeric salts or derivatives thus obtained, e.g. on the basis

of their differences in solubility, whilst the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents. Optically active acids in common use are e.g. the D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-o-tolyltartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid, N-acetylglutamic acid, aspartic acid, N-acetylaspartic acid or quinic acid. An optically active alcohol may be for example (+)- or (-)-menthol and an optically active acyl group in amides, for example, may be a (+)- or (-)-menthyloxycarbonyl group.

Furthermore, the compounds of formula I obtained may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts with inorganic or organic acids. Acids which may be used for this purpose include for example hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid, maleic acid or methanesulphonic acid.

Moreover, if the new compounds of formula I thus obtained contain a carboxy group, they may subsequently, if desired, be converted into the salts thereof with inorganic or organic bases, particularly for pharmaceutical use into the physiologically acceptable salts thereof. Suitable bases for this purpose include for example sodium hydroxide, potassium hydroxide, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

The compounds of general formulae VII to XII used as starting materials are known from the literature in some cases or may be obtained by methods known from the literature or may be obtained by the methods described hereinbefore and in the Examples. For example, the compounds of general formula VI are described in German Patent Application

198 24 922.5.

Moreover, the compounds of general formula XI may be obtained from the compounds of general formula I wherein R<sub>4</sub> denotes a C<sub>1-4</sub>-alkyl-phenyl group substituted in the alkyl moiety by a hydroxy group, for example, by reacting with alkyl- or arylsulphonyl - chlorides.

As already mentioned, the new compounds of general formula I wherein R<sub>1</sub> denotes a hydrogen atom or a prodrug group have valuable pharmacological properties, particularly inhibitory effects on various kinases, especially on receptor-tyrosine kinases such as VEGFR2, PDGFR $\alpha$ , PDGFR $\beta$ , FGFR1, FGFR3, EGFR, HER2, IGF1R and HGFR, as well as on complexes of CDK's (Cyclin Dependent Kinases) such as CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK8 and CDK9 with their specific cyclins (A, B1, B2, C, D1, D2, D3, E, F, G1, G2, H, I and K) and on viral cyclin, on the proliferation of cultivated human cells, particularly endothelial cells, e.g. in angiogenesis, but also on the proliferation of other cells, particularly tumour cells.

The biological properties of the new compounds were tested by the following standard procedure, as follows:

Human umbilical endothelial cells (HUVEC) were cultivated in IMDM (Gibco BRL), supplemented with 10 % foetal calf serum (FBS) (Sigma), 50  $\mu$ M of  $\beta$ -mercaptoethanol (Fluka), standard antibiotics, 15  $\mu$ g/ml of endothelial cell growth factor (ECGS, Collaborative Biomedical Products) and 100  $\mu$ g/ml of heparin (Sigma) on gelatine-coated culture dishes (0.2 % gelatine, Sigma) at 37°C, under 5 % CO<sub>2</sub> in a water-saturated atmosphere.

In order to investigate the inhibitory activity of the compounds according to the invention the cells were starved for 16 hours, i.e. kept in culture medium without growth factors (ECGS + heparin). The cells were detached from the culture dishes using trypsin/EDTA and washed once in serum-containing medium. Then they were seeded out in amounts of 2.5 x 10<sup>3</sup> cells per well.

The proliferation of the cells was stimulated with 5 ng/ml of VEGF<sub>165</sub> (vascular endothelial growth factor; H. Weich, GBF Braunschweig) and 10  $\mu$ g/ml of heparin. As a control, 6 wells in each dish were not stimulated.

The compounds according to the invention were dissolved in 100% dimethylsulphoxide and added to the cultures in various dilutions in triplicate, the maximum dimethyl sulphoxide concentration being 0.3 %.

- 5    The cells were incubated for 76 hours at 37°C, then for a further 16 hours <sup>3</sup>H-thymidine (0.1 µ Ci/well, Amersham) was added in order to determine the DNA synthesis. Then the radioactively labelled cells were immobilised on filter mats and the radioactivity incorporated was measured in a β-counter. In order to determine the inhibitory activity of the compounds according to the invention the mean value of the non-stimulated cells was  
10   subtracted from the mean value of the factor-stimulated cells (in the presence or absence of the compounds according to the invention).

The relative cell proliferation was calculated as a percentage of the control (HUVEC without inhibitor) and the concentration of active substance which inhibits the proliferation  
15   of the cells by 50 % (IC<sub>50</sub>) was determined.

The test results of the following compounds (a) to (s) of general formula I are given by way of example:

- 20   (a) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,
- (b) 3-Z-[(1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene)-6-carbamoyl-2-indolinone,
- 25   (c) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,
- (d) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-  
30   indolinone,

(e) 3-Z-[1-(4-((2,6-dimethyl-piperidin-1-yl)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

(f) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-  
5 6-ethoxycarbonyl-2-indolinone,

(g) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

10 (h) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

(i) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

15 (j) 3-Z-[1-(4-(N-acetyl-N-dimethylaminocarbonylmethyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(k) 3-Z-[1-(4-ethylaminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-  
20 indolinone,

(l) 3-Z-[1-(4-(1-methyl-imidazol-2-yl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

25 (m) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(n) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

30

(o) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(p) 3-Z-[1-(4-(N-dimethylaminocarbonylmethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(q) 3-Z-[1-(4-(N-((2-dimethylamino-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(r) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone and

(s) 3-Z-[1-(4-methylaminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone.



The following Table contains the results found:

Compound	IC <sub>50</sub> [μm]
(a)	0.04
(b)	0.35
(c)	0.01
(d)	0.02
(e)	0.05
(f)	0.01
(g)	0.003
(h)	0.01
(i)	0.03
(j)	0.02
(k)	0.03
(l)	0.1
(m)	0.02
(n)	0.02
(o)	0.01
(p)	0.02
(q)	0.02
(r)	0.01
(s)	0.04

In view of their inhibitory effect on the proliferation of cells, particularly endothelial cells  
 5 and tumour cells, the compounds of general formula I are suitable for treating diseases in  
 which the proliferation of cells, particularly endothelial cells, plays a part.

Thus, for example, the proliferation of endothelial cells and the concomitant  
 neovascularisation constitute a crucial stage in tumour progression (Folkman J. et al.,

Nature 339, 58-61, (1989); Hanahan D. and Folkman J., Cell 86, 353-365, (1996)).

Furthermore, the proliferation of endothelial cells is also important in haemangiomas, in metastatisation, rheumatoid arthritis, psoriasis and ocular neovascularisation (Folkman J., Nature Med. 1, 27-31, (1995)). The therapeutic usefulness of inhibitors of endothelial cell proliferation was demonstrated in the animal model for example by O'Reilly et al. and Parangi et al. (O'Reilly M.S. et al., Cell 88, 277-285, (1997); Parangi S. et al., Proc Natl Acad Sci USA 93, 2002-2007, (1996)).

The compounds of general formula I, their tautomers, their stereoisomers or the physiologically acceptable salts thereof are thus suitable, for example, for treating tumours (e.g. plate epithelial carcinoma, astrocytoma, Kaposi's sarcoma, glioblastoma, lung cancer, bladder cancer, carcinoma of the neck, melanoma, ovarian cancer, prostate cancer, breast cancer, small-cell lung cancer, glioma, colorectal carcinoma, urogenital cancer and gastrointestinal carcinoma as well as haematological cancers, such as multiple myeloma), psoriasis, arthritis (e.g. rheumatoid arthritis), haemangioma, angiofibroma, eye diseases (e.g. diabetic retinopathy), neovascular glaucoma, kidney diseases (e.g. glomerulonephritis), diabetic nephropathy, malignant nephrosclerosis, thrombic microangiopathic syndrome, transplant rejections and glomerulopathy, fibrotic diseases (e.g. cirrhosis of the liver), mesangial cell proliferative diseases, arteriosclerosis and damage to the nerve tissue and also for inhibiting the reocclusion of blood vessels after treatment with a balloon catheter, in vascular prosthetics or after the insertion of mechanical devices for keeping blood vessels open (e.g. stents), or other diseases in which cell proliferation or angiogenesis are involved.

25

By reason of their biological properties the compounds according to the invention may be used on their own or in conjunction with other pharmacologically active compounds, for example in tumour therapy, in monotherapy or in conjunction with other anti-tumour therapeutic agents, for example in combination with topoisomerase inhibitors (e.g. etoposide), mitosis inhibitors (e.g. vinblastin, taxol), compounds which interact with nucleic acids (e.g. cis-platin, cyclophosphamide, adriamycin), hormone antagonists (e.g.

30

tamoxifen), inhibitors of metabolic processes (e.g. 5-FU etc.), cytokines (e.g. interferons), kinase inhibitors, antibodies, or in conjunction with radiotherapy, etc. These combinations may be administered either simultaneously or sequentially.

- 5 For pharmaceutical use the compounds according to the invention are generally used for warm-blooded vertebrates, particularly humans, in doses of 0.01-100 mg/kg of body weight, preferably 0.1-20 mg/kg. For administration they are formulated with one or more conventional inert carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, stearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof in conventional galenic preparations such as plain or coated tablets, capsules, powders, injectable solutions, ampoules, suspensions, solutions, sprays or suppositories.

15

The Examples which follow are intended to illustrate the invention:

Abbreviations used:

20

FMOC = 9-fluorenylmethoxycarbonyl

HOBt = 1-hydroxy-1H-benzotriazole

25

TBTU = O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium-tetrafluoroborate

DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

Preparation of the starting compounds:

Solid phase Example I

- 5 2.0 g of Rink resin (MBHA resin, made by Messrs Novabiochem) are left to swell in 30 ml of dimethylformamide. Then 40 ml of 30% piperidine in dimethylformamide are added and the mixture is shaken for 7 minutes to cleave the Fmoc protecting group. The resin is then washed repeatedly with dimethylformamide. Then 0.4 g of 2-indolinone-6-carboxylic acid (prepared analogously to Langenbeck et al., Justus Liebigs Ann. Chem. 499, 201-208  
10 (1932)), 297 mg HOBt, 706 mg TBTU and 0.9 ml of N-ethyl-diisopropylamine in 30 ml of dimethylformamide are added and the mixture is shaken for 1 hour. Then the solution is suction filtered and the resin is washed five times with 30 ml of dimethylformamide and three times with 30 ml of methylene chloride. To dry it, nitrogen is blown through the resin.
- 15 Yield: 1.9 g of charged resin

Solid phase example II

- 20 1.9 g of the resin obtained in Example I are stirred with 6 ml of acetic anhydride and 6 ml of triethyl orthobenzoate for 3 hours at 110°C. Then the mixture is left to cool and the resin is washed with dimethylformamide and subsequently with methylene chloride.
- Yield: 1.9 g of moist resin

The following charged resins are prepared analogously to Example II:

- 25 (1) resin charged with 3-Z-(1-ethoxy-methylene)-6-carbamoyl-2-indolinone  
Prepared by reacting the resin obtained according to Example I with triethyl orthoformate
- (2) resin charged with 3-Z-(1-methoxy-1-methyl-methylene)-6-carbamoyl-2-indolinone  
30 Prepared by reacting the resin obtained according to Example I with trimethyl orthoacetate

(3) resin charged with 3-Z-(1-methoxy-1-ethyl-methylene)-6-carbamoyl-2-indolinone  
Prepared by reacting the resin obtained according to Example I with trimethyl  
orthopropionate

- 5 (4) resin charged with 3-Z-(1-methoxy-1-propyl-methylene)-6-carbamoyl-2-indolinone  
Prepared by reacting the product of Example I and trimethyl orthobutyrate

### Example III

10 N-(4-nitrophenyl)-N-methyl-methanesulphonamide

---

3.0 g of N-methyl-4-nitroaniline are dissolved in 20 ml of pyridine and 2.4 g of  
methanesulphonic acid chloride added dropwise at room temperature. The mixture is  
stirred for 12 hours at room temperature. After this time the mixture is poured onto water,  
15 the precipitate formed is filtered off and dried at 50°C *in vacuo*.  
Yield: 4.0 g (87 % of theory),  
R<sub>f</sub> value: 0.5 (silica gel, ethyl acetate/toluene = 7:3)  
Melting point: 107-108 °C

20 Example IV

N-(2-dimethylamino-ethyl)-N-methylsulphonyl-4-nitroaniline

---

38.9 g of N-methylsulphonyl-4-nitroaniline are dissolved in 2.0 l of acetone, 51.9 g of 1-  
25 chloro-2-dimethylamino-ethane, 77.4 g of potassium carbonate and 5.0 g of sodium iodide  
are added and the mixture is stirred for a total of 4 days at 50°C, while after 12 hours a  
further 25.9 g of 1-chloro-2-dimethylamino-ethane, 49.8 g of potassium carbonate and 5.0  
g of sodium iodide in 500 ml of acetone are added and after 36 hours another 26.0 g of 1-  
chloro-2-dimethylamino-ethane, 50.0 g of potassium carbonate and 5.0 g of sodium iodide  
30 in 100 ml of acetone are added. After this time the mixture is filtered and the filtrate  
evaporated down. The residue is stirred with ether, suction filtered and dried at 40°C.

Yield: 25.3 g (49 % of theory),

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol/ammonia = 9:1:0.1)

C<sub>11</sub>H<sub>17</sub>N<sub>3</sub>O<sub>4</sub>S

ESI mass spectrum: m/z = 288 [M+H<sup>+</sup>]

5

The following compounds are prepared analogously to Example IV:

(1) 4-[N-(3-dimethylamino-propyl)-N-methylsulphonyl-amino]-nitrobenzene

10 (2) N-carboxymethyl-N-methylsulphonyl-4-nitroaniline

(3) N-cyanomethyl-N-methylsulphonyl-p-phenylenediamine

(4) 4-[N-(2-(N-benzyl-N-methyl-amino)-ethyl)-N-methylsulphonyl-amino]-nitrobenzene

15

(5) 4-[N-(3-phthalimido-2-yl-propyl)-N-methylsulphonyl-amino]-nitrobenzene

(6) 4-[N-(3-(N-benzyl-N-methyl-amino)-propyl)-N-methylsulphonyl-amino]-nitrobenzene

20 Example V

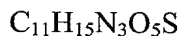
N-(dimethylaminocarbonyl-methyl)-N-methylsulphonyl-4-nitroaniline

---

25 7.0 g of N-carboxymethyl-N-methylsulphonyl-4-nitroaniline, 2.5 g of dimethylamine hydrochloride, 8.1 g of TBTU and 3.9 g of HOBT are dissolved in 125 ml of dimethylformamide and at 0°C 17.6 ml of N-ethyl-diisopropylamine are added. The mixture is stirred for 4 hours at room temperature, diluted with 1 l of water and the precipitate formed is suction filtered. After washing with water, ethanol and ether the residue is dried at 70°C *in vacuo*.

30 Yield: 5.3 g (69 % of theory),

R<sub>f</sub> value: 0.40 (silica gel, methylene chloride/methanol = 9:1)



ESI mass spectrum:  $m/z = 300$   $[\text{M-H}]^-$

The following compounds are prepared analogously to Example V:

5

(1) 4-[(N-dimethylaminocarbonylmethyl)-amino]-nitrobenzene

prepared from 4-(N-carboxymethyl-amino)-nitrobenzene and dimethylamine hydrochloride

10

(2) 4-(N-methylaminocarbonylmethyl-N-methylsulphonyl-amino)-nitrobenzene

Prepared from N-carboxymethyl-N-methylsulphonyl-4-nitroaniline and methylamine hydrochloride

(3) 4-[(N-(methylcarbamoyl-methyl)-N-methyl-amino)-methyl]-nitrobenzene

15

Prepared from 4-[(N-carboxymethyl-N-methyl-amino)-methyl]-nitrobenzene and methylamine hydrochloride

(4) 4-[(N-(dimethylcarbamoyl-methyl)-N-methyl-amino)-methyl]-nitrobenzene

Prepared from 4-[(N-carboxymethyl-N-methyl-amino)-methyl]-nitrobenzene and dimethylamine hydrochloride

20

#### Example VI

4-[N-(2-dimethylamino-ethyl)-N-acetyl-amino]-nitrobenzene

25

3.6 g of 4-(2-dimethylamino-ethylamino)-nitrobenzene (according to Gabbay et al., J. Am. Chem. Soc. 91, 5136 (1969)) are dissolved in 50 ml of methylene chloride and 5.0 ml of triethylamine are added. 1.3 ml of acetyl chloride are slowly added dropwise to this mixture at room temperature and the mixture is stirred for 2 hours at room temperature.

30

After this time another 5.0 ml of triethylamine and 1.3 ml of acetylchloride are added and the mixture is refluxed for another 2 hours. The solvent is removed, the residue is taken up

in ethyl acetate and the organic phase is extracted twice with water. After drying over  $\text{MgSO}_4$  the solvent is removed and the residue dried *in vacuo*.

Yield: 2.0 g (45 % of theory),

$R_f$  value: 0.55 (silica gel, methylene chloride/methanol/ammonia = 9:1:0.1)

5  $\text{C}_{12}\text{H}_{17}\text{N}_3\text{O}_3$

ESI mass spectrum:  $m/z = 252$   $[\text{M}+\text{H}^+]$

The following compounds are prepared analogously to Example VI:

10 (1) 4-[N-(3-dimethylamino-propyl)-N-acetyl-amino]-nitrobenzene

Prepared from 4-(3-dimethylamino-propylamino)-nitrobenzene (according to Gabbay et al., J. Am. Chem. Soc. 91, 5136 (1969) and acetyl chloride

(2) 4-[N-(2-dimethylamino-ethyl)-N-propionyl-amino]-nitrobenzene

15 Prepared from 4-(2-dimethylamino-ethylamino)-nitrobenzene and propionyl chloride

(3) 4-[N-acetyl-N-(dimethylaminocarbonylmethyl)-amino]-nitrobenzene

Prepared from 4-[N-(dimethylaminocarbonylmethyl)-amino]-nitrobenzene and acetyl chloride

20

(4) 4-[N-(2-dimethylamino-ethyl)-N-butyryl-amino]-nitrobenzene

Prepared from 4-(2-dimethylamino-ethylamino)-nitrobenzene and butyryl chloride

(5) 4-[N-(2-dimethylamino-ethyl)-N-isobutyryl-amino]-nitrobenzene

25 Prepared from 4-(2-dimethylamino-ethylamino)-nitrobenzene and isobutyryl chloride

(6) 4-[N-(2-dimethylamino-ethyl)-N-benzoyl-amino]-nitrobenzene

Prepared from 4-(2-dimethylamino-ethylamino)-nitrobenzene and benzoyl chloride

30 (7) 4-[N-(2-dimethylamino-ethyl)-N-acetyl-amino]-1,3-dinitrobenzene

Prepared from 4-(2-dimethylamino-ethyl-amino)-1,3-dinitrobenzene and acetyl chloride



(8) 4-[N-(2-dimethylamino-ethyl)-N-(furan-2-carbonyl)-amino]-nitrobenzene

Prepared from 4-(2-dimethylamino-ethylamino)-nitrobenzene and furan-2-carbonyl chloride

5

(9) 4-[N-(2-dimethylamino-ethyl)-N-(2-methoxy-benzoyl)-amino]-nitrobenzene

Prepared from 4-(2-dimethylamino-ethylamino)-nitrobenzene and 2-methoxy-benzoyl chloride

10

(10) 4-[N-(2-dimethylamino-ethyl)-N-(pyridine-3-carbonyl)-amino]-nitrobenzene

Prepared from 4-(2-dimethylamino-ethylamino)-nitrobenzene and nicotinic acid chloride

(11) 4-[N-(2-dimethylamino-ethyl)-N-(phenyl-acetyl)-amino]-nitrobenzene

Prepared from 4-(2-dimethylamino-ethylamino)-nitrobenzene and phenylacetyl-chloride

15

(12) 4-[N-(2-dimethylamino-ethyl)-N-acetyl-amino]-3-bromo-nitrobenzene

Prepared from 4-[N-(2-dimethylamino-ethyl)-amino]-3-bromo-nitrobenzene and acetyl chloride

20

(13) N-acryloyl-N-methyl-4-nitro-aniline

Prepared from 4-methylamino-nitrobenzene and acrylic acid chloride

(14) N-acryloyl-N-isopropyl-4-nitro-aniline

Prepared from 4-isopropylamino-nitrobenzene and acrylic acid chloride

25

(15) N-acryloyl-N-benzyl-4-nitro-aniline

Prepared from 4-benzylamino-nitrobenzene and acrylic acid chloride

(16) N-bromoacetyl-N-methyl-4-nitro-aniline

30 Prepared from 4-methylamino-nitrobenzene and bromoacetyl chloride

(17) N-bromoacetyl-N-isopropyl-4-nitro-aniline

Prepared from 4-isopropylamino-nitrobenzene and bromoacetyl chloride

(18) N-bromoacetyl-N-benzyl-4-nitro-aniline

5 Prepared from 4-benzylamino-nitrobenzene and bromoacetyl chloride

### Example VII

N-(dimethylaminomethylcarbonyl)-N-methyl-4-nitro-aniline

---

10

1.8 g of dimethylamine hydrochloride and 5.5 g of potassium carbonate are placed in 80 ml of acetone and 4.2 g of N-bromoacetyl-N-methyl-4-nitroaniline are added in three batches at room temperature. The mixture is stirred for 12 hours at room temperature. After this time the mixture is filtered and the filtrate is evaporated down. The residue is dissolved in  
15 ethyl acetate, washed twice with water, dried over sodium sulphate and finally concentrated by rotary evaporation.

Yield: 2.8 g (79 % of theory),

R<sub>f</sub> value: 0.5 (silica gel, ethyl acetate/methanol = 7:3)

Melting point: 121-122°C

20

The following compounds are prepared analogously to Example VII:

(1) N-(piperidin-1-yl-methylcarbonyl)-N-methyl-4-nitroaniline

25 (2) N-(morpholin-4-yl-methylcarbonyl)-N-methyl-4-nitroaniline

(3) N-[(4-benzyl-piperazin-1-yl)-methylcarbonyl]-N-methyl-4-nitroaniline

(4) N-(pyrrolidin-1-yl-methylcarbonyl)-N-methyl-4-nitroaniline

30

(5) N-[(N-aminocarbonylmethyl-N-methyl-amino)-methylcarbonyl]-N-methyl-4-nitroaniline

(6) N-[(N-benzyl-N-methyl-amino)-methylcarbonyl]-N-methyl-4-nitroaniline

5

(7) N-[di-(2-methoxyethyl)-amino-methylcarbonyl]-N-methyl-4-nitroaniline

(8) N-(dimethylaminomethylcarbonyl)-N-isopropyl-4-nitro-aniline

10 (9) N-(piperidin-1-yl-methylcarbonyl)-N-isopropyl-4-nitro-aniline

(10) N-[(4-tert.butoxycarbonyl-piperazin-1-yl)-methylcarbonyl]-N-isopropyl-4-nitro-aniline

15 (11) N-[(N-benzyl-N-methyl-amino)-methylcarbonyl]-N-benzyl-4-nitro-aniline

(12) N-(dimethylaminomethylcarbonyl)-N-benzyl-4-nitro-aniline

(13) N-(piperidin-1-yl-methylcarbonyl)-N-benzyl-4-nitro-aniline

20

(14) N-[di-(2-hydroxyethyl)-amino-methylcarbonyl]-N-methyl-4-nitroaniline

(15) N-[(N-(2-methoxyethyl)-N-methyl-amino)-methylcarbonyl]-N-methyl-4-nitroaniline

25 (16) N-[(N-(2-dimethylamino-ethyl)-N-methyl-amino)-methylcarbonyl]-N-methyl-4-nitroaniline

(17) N-[(4-methyl-piperazin-1-yl)-methylcarbonyl]-N-methyl-4-nitroaniline

30 (18) N-[(imidazol-1-yl)-methylcarbonyl]-N-methyl-4-nitroaniline

(19) N-[(phthalimido-2-yl)-methylcarbonyl]-N-methyl-4-nitroaniline

### Example VIII

5 N-[(2-dimethylamino-ethyl)-carbonyl]-N-benzyl-4-nitro-aniline

---

0.5 g of dimethylamine hydrochloride, 1.1 ml of triethylamine and 1.2 g of N-acryloyl-N-benzyl-4-nitro-aniline are dissolved in 50 ml of methanol and stirred for 24 hours at room temperature. After this time the mixture is evaporated down. The residue is purified over  
 10 an aluminium oxide column (activity 2-3) with methylene chloride/ethanol 50:1 as eluant. Yield: 1.4 g (98 % of theory),

R<sub>f</sub> value: 0.8 (aluminium oxide, methylene chloride/ethanol = 20:1)

Melting point: 73°C

15 The following compounds are prepared analogously to Example VIII:

(1) N-[(2-dimethylamino-ethyl)-carbonyl]-N-isopropyl-4-nitro-aniline

Prepared from N-acryloyl-N-isopropyl-4-nitro-aniline and dimethylamine hydrochloride

20 (2) N-[(2-dimethylamino-ethyl)-carbonyl]-N-methyl-4-nitro-aniline

Prepared from N-acryloyl-N-methyl-4-nitro-aniline and dimethylamine hydrochloride

(3) N-[(2-(4-tert.butoxycarbonyl-piperazin-1-yl)-ethyl)-carbonyl]-N-methyl-4-nitro-aniline

Prepared from N-acryloyl-N-methyl-4-nitro-aniline and N-tert.butoxycarbonyl-piperazine

25

(4) N-[(2-(piperidin-1-yl)-ethyl)-carbonyl]-N-methyl-4-nitro-aniline

Prepared from N-acryloyl-N-methyl-4-nitro-aniline and piperidine

(5) N-[(2-(N-benzyl-N-methyl-amino)-ethyl)-carbonyl]-N-methyl-4-nitro-aniline

30 Prepared from N-acryloyl-N-methyl-4-nitro-aniline and N-benzyl-N-methyl-amine

Example IX

4-(4-methyl-piperazine-1-yl)-nitrobenzene

---

- 5 31.5 g of 4-chloro-1-nitrobenzene and 44.4 ml of 1-methylpiperazine are combined and stirred for 18 hours at 90°C. Then the solution is poured onto ice water and the precipitate formed is suction filtered, washed with water and recrystallised from ethanol/water 1:1. The residue is dried *in vacuo* at 75°C.  
Yield: 44.0 g (99 % of theory),  
10  $R_f$  value: 0.5 (silica gel, methylene chloride/methanol = 10:1)  
Melting point: 108-112°C

The following compounds are prepared analogously to Example IX:

- 15 (1) N-(2-dimethylaminoethyl)-N-methyl-4-nitroaniline  
Prepared from 1-fluoro-4-nitrobenzene and 1-dimethylamino-2-methylamino-ethane  
  
(2) N-(3-dimethylaminopropyl)-N-methyl-4-nitroaniline  
Prepared from 1-fluoro-4-nitrobenzene and 1-dimethylamino-3-methylamino-propane  
20  
  
(3) 4-(N-carboxymethyl-amino)-nitrobenzene  
Prepared from 1-fluoro-4-nitrobenzene and glycine  
  
(4) N-cyclohexyl-p-phenylenediamine  
25 Prepared from 1-fluoro-4-nitrobenzene and cyclohexylamine  
  
(5) 6-[N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino]-3-phthalimido-2-yl-nitrobenzene  
Prepared from 2-nitro-4-phthalimido-2-yl-fluorobenzene,  
30 N-(2-dimethylamino-ethyl)-methanesulphonamide and sodium hydride as base

- (6) 6-[N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino]-1,3-dinitrobenzene  
Prepared from 2,4-dinitro-chlorobenzene, N-(2-dimethylamino-ethyl)-methanesulphonamide and sodium hydride as base
- 5 (7) 4-[N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino]-3-chloro-nitrobenzene  
Prepared from 2-fluoro-5-nitro-chlorobenzene, N-(2-dimethylamino-ethyl)-methanesulphonamide and sodium hydride as base
- (8) 4-(2-dimethylamino-ethyl-amino)-1,3-dinitrobenzene  
10 Prepared from 1-chloro-2,4-dinitro-benzene and N,N-dimethyl-ethylenediamine
- (9) 4-[N-(2-dimethylamino-ethyl)-N-(ethylsulphonyl)-amino]-nitrobenzene  
Prepared from 1-fluoro-4-nitro-benzene, N-(2-dimethylamino-ethyl)-ethanesulphonamide and sodium hydride as base
- 15 (10) 4-[N-(2-dimethylamino-ethyl)-N-(propylsulphonyl)-amino]-nitrobenzene  
Prepared from 1-fluoro-4-nitro-benzene, N-(2-dimethylamino-ethyl)-propanesulphonamide and sodium hydride as base
- 20 (11) 4-[N-(2-dimethylamino-ethyl)-N-(butylsulphonyl)-amino]-nitrobenzene  
Prepared from 1-fluoro-4-nitro-benzene, N-(2-dimethylamino-ethyl)-butanesulphonamide and sodium hydride as base
- (12) 4-[N-(2-dimethylamino-ethyl)-N-(benzylsulphonyl)-amino]-nitrobenzene  
25 Prepared from 1-fluoro-4-nitro-benzene, N-(2-dimethylamino-ethyl)-C-phenylmethanesulphonamide and sodium hydride as base
- (13) 4-[N-(2-dimethylamino-ethyl)-N-(phenylsulphonyl)-amino]-nitrobenzene  
Prepared from 1-fluoro-4-nitro-benzene, N-(2-dimethylamino-ethyl)-benzenesulphonamide  
30 and sodium hydride as base

(14) 4-[N-(2-dimethylamino-ethyl)-N-(isopropylsulphonyl)-amino]-nitrobenzene

Prepared from 1-fluoro-4-nitro-benzene, N-(2-dimethylamino-ethyl)-isopropylsulphonamide and sodium hydride as base

5 (15) 4-[N-(2-dimethylamino-ethyl)-amino]-3-bromo-nitrobenzene

Prepared from 2-bromo-1-fluoro-4-nitro-benzene and N,N-dimethyl-ethylenediamine

(16) 4-isopropylamino-nitrobenzene

Prepared from 1-fluoro-4-nitrobenzene and isopropylamine

10

(17) 4-benzylamino-nitrobenzene

Prepared from 1-fluoro-4-nitrobenzene and benzylamine

#### Example X

15

4-(imidazol-4-yl)-nitrobenzene

---

9.5 g of 2-phenylimidazole are carefully dissolved in 50 ml of concentrated sulphuric acid and 5.8 g of ammonium nitrate are added to this solution at 0°C. After a further 60 minutes stirring at 0°C the mixture is poured onto ice water, made basic with ammonia water and the precipitate formed is suction filtered and recrystallised from ethanol.

20

Yield: 8.0 g (64 % of theory),

R<sub>f</sub> value: 0.6 (silica gel, ethyl acetate/ethanol = 10:1)

C<sub>9</sub>H<sub>7</sub>N<sub>3</sub>O<sub>2</sub>

25

Mass spectrum: m/z = 189 [M<sup>+</sup>]

The following compounds are prepared analogously to Example X:

(1) 4-(imidazol-2-yl)-nitrobenzene

30

Prepared from 4-(imidazol-2-yl)-benzene

(2) 4-(5-methyl-imidazol-4-yl)-nitrobenzene

Prepared from 4-methyl-5-phenyl-imidazole (J. Heterocycl. Chem. 1983, 20, 1277-1281)

Example XI

5

4-(2-(imidazol-4-yl)-ethylene)-nitrobenzene

---

1.5 g of 4-nitrobenzaldehyde and 7.45 g of (N-trityl-imidazol-4-yl-methyl)-  
triphenylphosphonium chloride are dissolved in 75 ml of tetrahydrofuran and to this  
10 solution 3.0 ml of DBU are added dropwise at room temperature. After a further 120  
minutes stirring at room temperature the mixture is poured onto water and the precipitate  
formed is suction filtered. The product is taken up in 25 ml of 1N hydrochloric acid and  
refluxed for 4 hours. After this time it is neutralised with ammoniacal water, extracted with  
ethyl acetate and the organic phase is washed with water, dried over sodium sulphate and  
15 evaporated down. The residue is purified over a silica gel column with methylene  
chloride/methanol 10:1 as eluant.

Yield: 1.0 g of (47 % of theory),

R<sub>f</sub> value: 0.6 (silica gel, ethyl acetate/ethanol = 10:1)

Melting point: 185-188°C

20

Example XII

4-(piperidin-1-yl-methyl)-nitrobenzene

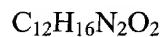
---

25 40.0 g of 4-nitrobenzyl bromide are dissolved in 500 ml of methylene chloride, 51.5 ml of  
triethylamine are added and 18.3 ml of piperidine are carefully added dropwise. After the  
end of the exothermic reaction the mixture is refluxed for another 30 minutes. After  
cooling it is washed with water and the organic phase is dried over sodium sulphate.  
Finally, the organic phase is evaporated down.

30 Yield: 36.3 g of (89 % of theory),

R<sub>f</sub> value: 0.6 (silica gel, methylene chloride/methanol = 9:1)





Mass spectrum:  $m/z = 221$  [ $\text{M}^+$ ]

The following compounds are prepared analogously to Example XII:

5

(1) 4-[(2,6-dimethyl-piperidin-1-yl)-methyl]-nitrobenzene

(2) 3-(N,N-dimethyl-aminomethyl)-nitrobenzene

10 (3) 4-(N,N-dimethyl-aminomethyl)-nitrobenzene

(4) 4-(2-dimethylamino-ethyl)-nitrobenzene

(5) 4-(2-diethylamino-ethyl)-nitrobenzene

15

(6) 4-(diethylamino-methyl)-nitrobenzene

(7) 4-(N-benzyl-N-methyl-aminomethyl)-nitrobenzene

20 (8) 4-(N-ethyl-N-methyl-aminomethyl)-nitrobenzene

(9) 4-[N-(n-hexyl)-N-methyl-aminomethyl]-nitrobenzene

(10) 4-(thiomorpholin-4-yl-methyl)-nitrobenzene

25

(11) 4-[(4-methyl-piperazine-1-yl)-methyl]-nitrobenzene

(12) 4-(imidazol-1-yl-methyl)-nitrobenzene

30 (13) 4-[2-(4-hydroxy-piperidin-1-yl)-ethyl-amino]-nitrobenzene

(14) 4-[(3-hydroxy-pyrrolidin-1-yl)-methyl]-nitrobenzene

(15) 4-(1,2,4-triazol-1-yl-methyl)-nitrobenzene

5 (16) 4-(1,2,3-triazol-2-yl-methyl)-nitrobenzene

(17) 4-(1,2,3-triazol-1-yl-methyl)-nitrobenzene

(18) 4-[(N-ethoxycarbonylmethyl-N-methyl-amino)-methyl]-nitrobenzene

10

(19) 4-[(N-aminocarbonylmethyl-N-methyl-amino)-methyl]-nitrobenzene

(20) 4-(azetidin-1-yl-methyl)-nitrobenzene

15 (21) 4-[(di-(2-methoxy-ethyl)-amino)-methyl]-nitrobenzene

(22) 4-[N-(N-tert.butoxycarbonyl-3-amino-propyl)-N-methyl-aminomethyl]-nitrobenzene

(23) 4-[(N-propyl-N-methyl-amino)-methyl]-nitrobenzene

20

(24) 4-[(N-(2-dimethylamino-ethyl)-N-methyl-amino)-methyl]-nitrobenzene

(25) 4-[(N-(3-dimethylamino-propyl)-N-methyl-amino)-methyl]-nitrobenzene

25 (26) 4-[(N-(2-methoxy-ethyl)-N-methyl-amino)-methyl]-nitrobenzene

(27) 4-[(N-(2-hydroxy-ethyl)-N-methyl-amino)-methyl]-nitrobenzene

(28) 4-[(N-(dioxolan-2-yl-methyl)-N-methyl-amino)-methyl]-nitrobenzene

30

(29) 4-(3-oxo-piperazine-1-yl-methyl)-nitrobenzene

Example XIII

4-[(N-carboxymethyl-N-methyl-amino)-methyl]-nitrobenzene

---

5

7.33 g of 4-[(N-ethoxycarbonylmethyl-N-methyl-amino)-methyl]-nitrobenzene are dissolved in 140 ml of ethanol, 34.0 ml of 1N sodium hydroxide solution are added and the mixture is stirred for half an hour at room temperature. After this time the mixture is neutralised with 34 ml of 1N hydrochloric acid, the solvent removed, the residue taken up in methylene chloride and extracted with water. The aqueous phase is evaporated down and the residue is recrystallised from methylene chloride.

10

Yield: 5.43 g (84 % of theory),

R<sub>f</sub> value: 0.4 (silica gel, methylene chloride/methanol = 2:1)

C<sub>10</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub>

15

Mass spectrum: m/z = 223 [M<sup>+</sup>]

Example XIV

4-(N-ethyl-aminomethyl)-nitrobenzene

---

20

6.0 g of 4-nitrobenzyl bromide are dissolved in 25 ml of ethanol, combined with 25 ml of 10% ethanolic ethylamine solution and refluxed for 2 hours. Then the solution is concentrated by rotary evaporation, the residue is taken up with methylene chloride and washed with dilute sodium hydroxide solution. Finally the organic phase is evaporated down.

25

Yield: 2.3 g (46 % of theory),

R<sub>f</sub> value: 0.2 (silica gel, methylene chloride/methanol = 9:1)

C<sub>9</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>

ESI mass spectrum: m/z = 179 [M-H<sup>-</sup>]

30

The following compounds are prepared analogously to Example XIV:

(1) 4-[N-(4-chlorobenzyl)-aminomethyl]-nitrobenzene

(2) 4-(N-cyclohexyl-aminomethyl)-nitrobenzene

5

(3) 4-(N-isopropyl-aminomethyl)-nitrobenzene

(4) 4-(N-propyl-aminomethyl)-nitrobenzene

10 (5) 4-(N-methyl-aminomethyl)-nitrobenzene

(6) 4-(N-butyl-aminomethyl)-nitrobenzene

(7) 4-(N-methoxycarbonylmethyl-aminomethyl)-nitrobenzene

15

(8) 4-(N-benzyl-aminomethyl)-nitrobenzene

(9) 4-(aminomethyl)-nitrobenzene

20 (10) 4-(pyrrolidin-1-yl-methyl)-nitrobenzene

(11) 4-(morpholin-4-yl-methyl)-nitrobenzene

(12) 4-(hexamethyleneiminomethyl)-nitrobenzene

25

(13) 4-(4-hydroxy-piperidin-1-yl-methyl)-nitrobenzene

(14) 4-(4-methoxy-piperidin-1-yl-methyl)-nitrobenzene

30 (15) 4-(4-methyl-piperidin-1-yl-methyl)-nitrobenzene

(16) 4-(4-ethyl-piperidin-1-yl-methyl)-nitrobenzene

(17) 4-(4-isopropyl-piperidin-1-yl-methyl)-nitrobenzene

5 (18) 4-(4-phenyl-piperidin-1-yl-methyl)-nitrobenzene

(19) 4-(4-benzyl-piperidin-1-yl-methyl)-nitrobenzene

(20) 4-(4-ethoxycarbonyl-piperidin-1-yl-methyl)-nitrobenzene

10

(21) 4-(N,N-dipropyl-aminomethyl)-nitrobenzene

(22) 4-(4-tert.butoxycarbonyl-piperazin-1-yl-methyl)-nitrobenzene

15 (23) 4-(2-morpholin-4-yl-ethyl)-nitrobenzene

(24) 4-(2-pyrrolidin-1-yl-ethyl)-nitrobenzene

(25) 4-(2-piperidin-1-yl-ethyl)-nitrobenzene

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(26) 4-(N-ethyl-N-benzyl-aminomethyl)-nitrobenzene

(27) 4-(N-propyl-N-benzyl-aminomethyl)-nitrobenzene

25 (28) 4-[N-methyl-N-(4-chlorobenzyl)-aminomethyl]-nitrobenzene

(29) 4-[N-methyl-N-(4-bromobenzyl)-aminomethyl]-nitrobenzene

(30) 4-[N-methyl-N-(4-fluorobenzyl)-aminomethyl]-nitrobenzene

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(31) 4-[N-methyl-N-(4-methylbenzyl)-aminomethyl]-nitrobenzene

(32) 4-[N-methyl-N-(3-chlorobenzyl)-aminomethyl]-nitrobenzene

(33) 4-[N-methyl-N-(3,4-dimethoxybenzyl)-aminomethyl]-nitrobenzene

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(34) 4-[N-methyl-N-(4-methoxybenzyl)-aminomethyl]-nitrobenzene

(35) 4-(N-2,2,2-trifluoroethyl-N-benzyl-aminomethyl)-nitrobenzene

10 (36) 4-[N-2,2,2-trifluoroethyl-N-(4-chlorobenzyl)-aminomethyl]-nitrobenzene

(37) 4-(thiomorpholin-4-yl-methyl)-nitrobenzene

(38) 4-(azetidin-1-yl-methyl)-nitrobenzene

15

(39) 4-(3,4-dihydropyrrolidin-1-yl-methyl)-nitrobenzene

(40) 4-(3,4-dihydropiperidin-1-yl-methyl)-nitrobenzene

20 (41) 4-(2-methoxycarbonyl-pyrrolidin-1-yl-methyl)-nitrobenzene

(42) 4-(3,5-dimethyl-piperidin-1-yl-methyl)-nitrobenzene

(43) 4-(4-phenyl-piperazin-1-yl-methyl)-nitrobenzene

25

(44) 4-(4-phenyl-4-hydroxy-piperidin-1-yl-methyl)-nitrobenzene

(45) 4-[N-(3,4,5-trimethoxybenzyl)-N-methyl-aminomethyl]-nitrobenzene

30 (46) 4-[N-(3,4-dimethoxybenzyl)-N-ethyl-aminomethyl]-nitrobenzene

- (47) 4-[N-(2,6-dichlorobenzyl)-N-methyl]-aminomethyl]-nitrobenzene
- (48) 4-[N-(4-trifluoromethylbenzyl)-N-methyl]-aminomethyl]-nitrobenzene
- 5 (49) 4-(N-benzyl-N-isopropyl-aminomethyl)-nitrobenzene
- (50) 4-(N-benzyl-N-tert.butyl-aminomethyl)-nitrobenzene
- (51) 4-(N,N-diisopropyl-aminomethyl)-nitrobenzene
- 10 (52) 4-(N,N-diisobutyl-aminomethyl)-nitrobenzene
- (53) 4-(2,3,4,5-tetrahydro-benzo(d)azepin-3-yl-methyl)-nitrobenzene
- (54) 4-(2,3-dihydro-isoindol-2-yl-methyl)-nitrobenzene
- 15 (55) 4-(6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-nitrobenzene
- (56) 4-(1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-nitrobenzene
- 20 (57) 4-[N-(2-hydroxyethyl)-N-benzyl-aminomethyl]-nitrobenzene
- (58) 4-[N-(1-ethyl-pentyl)-N-(pyridin-2-yl-methyl)-aminomethyl]-nitrobenzene
- 25 (59) 4-(piperin-1-yl-methyl)-1,3-dinitrobenzene
- (60) 4-(N-phenethyl-N-methyl-aminomethyl)-nitrobenzene
- (61) 4-[N-(3,4-dihydroxy-phenethyl)-N-methyl-aminomethyl]-nitrobenzene
- 30 (62) 4-[N-(3,4,5-trimethoxy-phenethyl)-N-methyl-aminomethyl]-nitrobenzene

(63) 4-[N-(3,4-dimethoxy-phenethyl)-N-methyl-aminomethyl]-nitrobenzene

(64) 4-[N-(3,4-dimethoxy-benzyl)-N-methyl-aminomethyl]-nitrobenzene

5

(65) 4-[N-(4-chloro-benzyl)-N-methyl-aminomethyl]-nitrobenzene

(66) 4-[N-(4-bromo-benzyl)-N-methyl-aminomethyl]-nitrobenzene

10 (67) 4-[N-(4-fluoro-benzyl)-N-methyl-aminomethyl]-nitrobenzene

(68) 4-[N-(4-methyl-benzyl)-N-methyl-aminomethyl]-nitrobenzene

(69) 4-[N-(4-nitro-phenethyl)-N-methyl-aminomethyl]-nitrobenzene

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(70) 4-(N-phenethyl-N-benzyl-aminomethyl)-nitrobenzene

(71) 4-(N-phenethyl-N-cyclohexyl-aminomethyl)-nitrobenzene

20 (72) 4-[N-(2-(pyridin-2-yl)-ethyl)-N-methyl-aminomethyl]-nitrobenzene

(73) 4-[N-(2-(pyridin-4-yl)-ethyl)-N-methyl-aminomethyl]-nitrobenzene

(74) 4-[N-(pyridin-4-yl-methyl)-N-methyl-aminomethyl]-nitrobenzene

25

(75) 4-(N,N-dibenzyl-aminomethyl)-nitrobenzene

(76) 4-[N-(4-nitro-phenethyl)-N-propyl-aminomethyl]-nitrobenzene

30 (77) 4-(N-benzyl-N-(3-cyano-propyl)-aminomethyl)-nitrobenzene



(78) 4-(N-benzyl-N-allyl-aminomethyl)-nitrobenzene

(79) 4-[N-benzyl-N-(2,2,2-trifluoroethyl)-aminomethyl]-nitrobenzene

5 (80) 4-[N-(2-benzo(1,3)dioxol-5-yl-methyl)-N-methyl-aminomethyl]-nitrobenzene

(81) 4-(7-chloro-2,3,4,5-tetrahydro-benzo(d)azepin-3-yl-methyl)-nitrobenzene

(82) 4-(7,8-dichloro-2,3,4,5-tetrahydro-benzo(d)azepin-3-yl-methyl)-nitrobenzene

10

(83) 4-(7-methoxy-2,3,4,5-tetrahydro-benzo(d)azepin-3-yl-methyl)-nitrobenzene

(84) 4-(7-methyl-2,3,4,5-tetrahydro-benzo(d)azepin-3-yl-methyl)-nitrobenzene

15 (85) 4-(7,8-dimethoxy-2,3,4,5-tetrahydro-benzo(d)azepin-3-yl-methyl)-nitrobenzene

(86) 4-(6,7-dichloro-1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-nitrobenzene

(87) 4-(6,7-dimethyl-1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-nitrobenzene

20

(88) 4-(6-chloro-1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-nitrobenzene

(89) 4-(7-chloro-1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-nitrobenzene

25 (90) 4-(6-methoxy-1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-nitrobenzene

(91) 4-(7-methoxy-1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-nitrobenzene

(92) 4-[(2,3,4,5-tetrahydro-azepino(4,5-b)pyrazin-3-yl)-methyl]-nitrobenzene

30

(93) 4-[(7-amino-2,3,4,5-tetrahydro-azepino(4,5-b)pyrazin-3-yl)-methyl]-nitrobenzene

(94) 4-[(2-amino-5,6,7,8-tetrahydro-azepino(4,5-d)thiazol-6-yl)-methyl]-nitrobenzene

(95) 4-[(5,6,7,8-tetrahydro-azepino(4,5-d)thiazol-6-yl)-methyl]-nitrobenzene

5

Example XV

4-(1,1-dioxo-thiomorpholin-4-yl-methyl)-nitrobenzene

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- 10 6.0 g of 4-(thiomorpholin-4-yl-methyl)-nitrobenzene are dissolved in 100 ml of methylene chloride and 10.3 g of meta-chloroperbenzoic acid are slowly added. After a further 3 hours stirring at room temperature the precipitate obtained is filtered off.

Yield: 6.2 g (91 % of theory)

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 1:1)

- 15 C<sub>11</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>S

Mass spectrum: m/z = 270 [M<sup>+</sup>]

The following compound is prepared analogously to Example XV:

- 20 (1) 4-(1-oxo-thiomorpholin-4-yl-methyl)-nitrobenzene

Example XVI

4-[N-(3-amino-propyl)-N-methylsulphonyl-amino]-nitrobenzene

---

25

- 9.5 g of 4-[N-(3-phthalimido-2-yl-propyl)-N-methylsulphonyl-amino]-nitrobenzene are dissolved in 200 ml of ethanol, 11.5 ml of hydrazine hydrate are added and the mixture is stirred for 1.5 hours at 50 °C. After cooling the residue is largely evaporated down, water is added and the solution is extracted with methylene chloride. The organic phase is dried,  
30 evaporated down and purified over a silica gel column with methylene chloride/methanol/ammonia 9:1:0.1.

Yield: 2.5 g (39 % of theory)

R<sub>f</sub> value: 0.2 (silica gel, methylene chloride/methanol = 9:1)

C<sub>10</sub>H<sub>15</sub>N<sub>3</sub>O<sub>4</sub>S

ESI mass spectrum: m/z = 272 [M-H]

5

The following compound is prepared analogously to Example XVI:

(1) 6-[N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino]-3-amino-nitrobenzene

Prepared from 6-[N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino]-3-phthalimido-2-yl-nitrobenzene

10

#### Example XVII

4-(1-methyl-imidazol-2-yl)-nitrobenzene

15

7.5 g of 4-(imidazol-2-yl)-nitrobenzene are dissolved in 50 ml of dimethylsulphoxide and at 0°C 5.0 g of potassium tert.butoxide are added. After one hour of stirring at room temperature 2.6 ml of methyl iodide are added dropwise and the mixture is stirred for one hour at room temperature. After this time the residue is poured onto ice water and the precipitate formed is suction filtered, washed with water and dried.

20

Yield: 6.1 g (76 % of theory)

R<sub>f</sub> value: 0.6 (silica gel, methylene chloride/methanol = 10:1)

Melting point: 186-187°C

25 The following compounds are prepared analogously to Example XVII:

(1) 4-(1-ethyl-imidazol-2-yl)-nitrobenzene

Prepared from 4-(imidazol-2-yl)-nitrobenzene and ethyl iodide

30 (2) 4-(1-benzyl-imidazol-2-yl)-nitrobenzene

Prepared from 4-(imidazol-2-yl)-nitrobenzene and benzyl bromide

Example XVIII

4-[(N-(2-(2-methoxy-ethoxy)-ethyl)-N-methyl-amino)-methyl]-nitrobenzene

- 5 5.0 g of 4-methylaminomethyl-nitrobenzene are dissolved in 30 ml of dimethylformamide and 4.6 g of 2-(2-methoxy-ethoxy)-ethyl chloride are added. After six hours' stirring at 100°C the solvent is removed and the residue is taken up in ethyl acetate. The organic phase is washed with water and dried over sodium sulphate. After the elimination of the solvent the residue is purified over an aluminium oxide column (activity 2-3) with  
10 toluene/ethyl acetate 5:1 as eluant.

Yield: 2.3 g (29 % of theory)

R<sub>f</sub> value: 0.5 (aluminium oxide, toluene/ethyl acetate = 5:1)

C<sub>13</sub>H<sub>20</sub>N<sub>2</sub>O<sub>4</sub>

ESI mass spectrum: m/z = 267 [M-H]<sup>+</sup>

Example XIX

4-(N-ethyl-N-tert.butoxycarbonyl-aminomethyl)-nitrobenzene

---

- 20 2.2 g of 4-(ethylaminomethyl)-nitrobenzene are dissolved in 50 ml of ethyl acetate and stirred with 2.6 g of di-tert-butyl. dicarbonate (tert.butoxycarbonyl-anhydride) for 30 minutes at room temperature. Then the solution is washed with water and evaporated down.

Yield: 3.4 g of theory

- 25 R<sub>f</sub> value: 0.3 (silica gel, methylene chloride/methanol = 50:1)

Melting point: 85 °C

The following compounds are prepared analogously to Example XIX:

- 30 (1) 4-[N-(4-chlorophenyl-methyl)-N-tert.butoxycarbonyl-aminomethyl]-nitrobenzene

(2) 4-(N-tert.butoxycarbonyl-aminomethyl)-nitrobenzene

(3) 4-(N-cyclohexyl-N-tert.butoxycarbonyl-aminomethyl)-nitrobenzene

5 (4) 4-(N-isopropyl-N-tert.butoxycarbonyl-aminomethyl)-nitrobenzene

(5) 4-(N-methyl-N-tert.butoxycarbonyl-aminomethyl)-nitrobenzene

(6) 4-(N-propyl-N-tert.butoxycarbonyl-aminomethyl)-nitrobenzene

10

(7) 4-(N-butyl-N-tert.butoxycarbonyl-aminomethyl)-nitrobenzene

(8) 4-(N-methoxycarbonylmethyl-N-tert.butoxycarbonyl-aminomethyl)-nitrobenzene

15 (9) 4-(N-benzyl-N-tert.butoxycarbonyl-aminomethyl)-nitrobenzene

(10) 4-[N-(3-trifluoroacetyl-amino-propyl)-N-methylsulphonyl-amino]-nitrobenzene

Prepared from 4-[N-(3-amino-propyl)-N-methylsulphonyl-amino]-nitrobenzene and trifluoroacetic acid anhydride

20

(11) 4-[(4-tert.butoxycarbonyl-piperazin-1-yl)-methyl]-nitrobenzene

#### Example XX

25 4-(piperidin-1-yl-methyl)-aniline

---

37.0 g of 4-(piperidin-1-yl-methyl)-nitrobenzene are dissolved in 300 ml of methanol, 8.0 g of Raney nickel are added and the mixture is hydrogenated for 85 minutes with 3 bars of hydrogen at room temperature. The catalyst is filtered off and the filtrate is evaporated

30 down.

Yield: 24.0 g (75 % of theory),

R<sub>f</sub> value: 0.4 (silica gel, methylene chloride/methanol = 9:1)

C<sub>12</sub>H<sub>18</sub>N<sub>2</sub>

ESI mass spectrum: m/z = 191 [M+H<sup>+</sup>]

5 The following compounds are prepared analogously to Example VIII:

(1) 4-[(2,6-dimethyl-piperidin-1-yl)-methyl]-aniline

(2) N-(2-dimethylamino-ethyl)-N-methylsulphonyl-p-phenylenediamine

10

(3) 3-(dimethylaminomethyl)-aniline

(4) 4-(dimethylaminomethyl)-aniline

15

(5) 4-(2-dimethylamino-ethyl)-aniline

(6) 4-[N-(2-dimethylamino-ethyl)-N-acetyl-amino]-aniline

(7) 4-[N-(3-dimethylamino-propyl)-N-acetyl-amino]-aniline

20

(8) 4-[N-(2-dimethylamino-ethyl)-N-benzoyl-amino]-aniline

(9) 4-[N-(2-dimethylamino-ethyl)-N-propionyl-amino]-aniline

25

(10) 4-[N-(2-dimethylamino-ethyl)-N-butyryl-amino]-aniline

(11) 4-[N-(2-dimethylamino-ethyl)-N-isobutyryl-amino]-aniline

(12) 4-(N-tert.butoxycarbonyl-aminomethyl)-aniline

30

(13) 4-(N-ethyl-N-tert.butoxycarbonyl-aminomethyl)-aniline

(14) 4-[N-(4-chlorophenyl-methyl)-N-tert.butoxycarbonyl-aminomethyl]-aniline

(15) 4-(N-cyclohexyl-N-tert.butoxycarbonyl-aminomethyl)-aniline

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(16) 4-(N-isopropyl-N-tert.butoxycarbonyl-aminomethyl)-aniline

(17) 4-(N-propyl-N-tert.butoxycarbonyl-aminomethyl)-aniline

10 (18) 4-(N-methyl-N-tert.butoxycarbonyl-aminomethyl)-aniline

(19) 4-(N-butyl-N-tert.butoxycarbonyl-aminomethyl)-aniline

(20) 4-(N-methoxycarbonyl-methyl-N-tert.butoxycarbonyl-aminomethyl)-aniline

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(21) 4-(N-benzyl-N-tert.butoxycarbonyl-aminomethyl)-aniline

(22) 4-(pyrrolidin-1-yl-methyl)-aniline

20 (23) 4-(morpholin-4-yl-methyl)-aniline

(24) 4-(hexamethyleneiminomethyl)-aniline

(25) 4-(4-hydroxy-piperidin-1-yl-methyl)-aniline

25

(26) 4-(4-methoxy-piperidin-1-yl-methyl)-aniline

(27) 4-(4-methyl-piperidin-1-yl-methyl)-aniline

30 (28) 4-(4-ethyl-piperidin-1-yl-methyl)-aniline

(29) 4-(4-isopropyl-piperidin-1-yl-methyl)-aniline

(30) 4-(4-phenyl-piperidin-1-yl-methyl)-aniline

5 (31) 4-(4-benzyl-piperidin-1-yl-methyl)-aniline

(32) 4-(4-ethoxycarbonyl-piperidin-1-yl-methyl)-aniline

(33) 4-(N,N-dipropyl-aminomethyl)-aniline

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(34) 4-(4-tert.butoxycarbonyl-piperazin-1-yl-methyl)-aniline

(35) 4-(2-morpholin-4-yl-ethyl)-aniline

15

(36) 4-(2-pyrrolidin-1-yl-ethyl)-aniline

(37) 4-(2-piperidin-1-yl-ethyl)-aniline

(38) 4-(N-propyl-N-benzyl-aminomethyl)-aniline

20

(39) 4-[N-(n-hexyl)-N-methyl-aminomethyl]-aniline

(40) 4-[N-methyl-N-(4-chlorobenzyl)-aminomethyl]-aniline

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(41) 4-[N-methyl-N-(4-bromobenzyl)-aminomethyl]-aniline

(42) 4-[N-methyl-N-(4-methylbenzyl)-aminomethyl]-aniline

(43) 4-[N-methyl-N-(4-fluorobenzyl)-aminomethyl]-aniline

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(44) 4-[N-methyl-N-(3-chlorobenzyl)-aminomethyl]-aniline



(45) 4-[N-methyl-N-(3,4-dimethoxybenzyl)-aminomethyl]-aniline

(46) 4-[N-methyl-N-(4-methoxybenzyl)-aminomethyl]-aniline

5

(47) 4-(N-2,2,2-trifluoroethyl-N-benzyl-aminomethyl)-aniline

(48) 4-[N-2,2,2-trifluoroethyl-N-(4-chlorobenzyl)-aminomethyl]-aniline

10 (49) 4-(thiomorpholin-4-yl-methyl)-aniline

(50) 4-(1-oxo-thiomorpholin-4-yl-methyl)-aniline

(51) 4-(1,1-dioxo-thiomorpholin-4-yl-methyl)-aniline

15

(52) 4-(azetidion-1-yl-methyl)-aniline

(53) 4-(3,4-dihydropyrrolidin-1-yl-methyl)-aniline

20 (54) 4-(3,4-dihydropiperidin-1-yl-methyl)-aniline

(55) 4-(2-methoxycarbonyl-pyrrolidin-1-yl-methyl)-aniline

(56) 4-(3,5-dimethyl-piperidin-1-yl-methyl)-aniline

25

(57) 4-(4-phenyl-piperazin-1-yl-methyl)-aniline

(58) 4-(4-phenyl-4-hydroxy-piperidin-1-yl-methyl)-aniline

30 (59) 4-[N-(3,4,5-trimethoxy-benzyl)-N-methyl-aminomethyl]-aniline

(60) 4-[N-(3,4-dimethoxy-benzyl)-N-ethyl-aminomethyl]-aniline

(61) 4-(N-benzyl-N-ethyl-aminomethyl)-aniline

5 (62) 4-[N-(2,6-dichlorobenzyl)-N-methyl-aminomethyl]-aniline

(63) 4-[N-(4-trifluoromethylbenzyl)-N-methyl-aminomethyl]-aniline

(64) 4-(N-benzyl-N-isopropyl-aminomethyl)-aniline

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(65) 4-(N-benzyl-N-tert.butyl-aminomethyl)-aniline

(66) 4-(diethylamino-methyl)-aniline

15 (67) 4-(2-diethylamino-ethyl)-aniline

(68) 4-(N,N-diisopropyl-aminomethyl)-aniline

(69) 4-(N,N-diisobutyl-aminomethyl)-aniline

20

(70) 4-(2,3,4,5-tetrahydro-benzo(d)azepin-3-yl-methyl)-aniline

(71) 4-(2,3-dihydro-isoindol-2-yl-methyl)-aniline

25 (72) 4-(6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-aniline

(73) 4-(1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-aniline

(74) 4-[N-(2-hydroxy-ethyl)-N-benzyl-aminomethyl]-aniline

30

(75) 4-[N-(1-ethyl-pentyl)-N-(pyridin-2-yl-methyl)-aminomethyl]-aniline

(76) 4-(piperidin-1-yl-methyl)-3-nitro-aniline

(77) 4-(piperidin-1-yl-methyl)-3-amino-aniline

5

(78) 4-(N-benzyl-N-methyl-aminomethyl)-aniline

(79) 4-(N-ethyl-N-methyl-aminomethyl)-aniline

10 (80) 4-(N-phenethyl-N-methyl-aminomethyl)-aniline

(81) 4-[N-(3,4-dihydroxy-phenethyl)-N-methyl-aminomethyl]-aniline

(82) 4-[N-(3,4,5-trimethoxy-phenethyl)-N-methyl-aminomethyl]-aniline

15

(83) 4-[N-(3,4-dimethoxy-phenethyl)-N-methyl-aminomethyl]-aniline

(84) 4-[N-(3,4-dimethoxy-benzyl)-N-methyl-aminomethyl]-aniline

20 (85) 4-[N-(4-chloro-benzyl)-N-methyl-aminomethyl]-aniline

(86) 4-[N-(4-bromo-benzyl)-N-methyl-aminomethyl]-aniline

(87) 4-[N-(4-fluoro-benzyl)-N-methyl-aminomethyl]-aniline

25

(88) 4-[N-(4-methyl-benzyl)-N-methyl-aminomethyl]-aniline

(89) 4-[N-(4-nitro-phenethyl)-N-methyl-aminomethyl]-aniline

30 (90) 4-(N-phenethyl-N-benzyl-aminomethyl)-aniline

(91) 4-(N-phenethyl-N-cyclohexyl-aminomethyl)-aniline

(92) 4-[N-(2-(pyridin-2-yl)-ethyl)-N-methyl-aminomethyl]-aniline

5 (93) 4-[N-(2-(pyridin-4-yl)-ethyl)-N-methyl-aminomethyl]-aniline

(94) 4-[N-(pyridin-4-yl-methyl)-N-methyl-aminomethyl]-aniline

(95) 4-(N,N-dibenzylaminomethyl)-aniline

10

(96) 4-[N-(4-nitro-benzyl)-N-propyl-aminomethyl]-aniline

(97) 4-[N-benzyl-N-(3-cyano-propyl)-aminomethyl]-aniline

15 (98) 4-(N-benzyl-N-allyl-aminomethyl)-aniline

(99) 4-[N-benzyl-N-(2,2,2-trifluoroethyl)-aminomethyl]-aniline

(100) 4-[(benzo(1,3)dioxol-5-yl-methyl)-methyl-aminomethyl]-aniline

20

(101) 4-(7-chloro-2,3,4,5-tetrahydro-benzo(d)azepin-3-yl-methyl)-aniline

(102) 4-(7,8-dichloro-2,3,4,5-tetrahydro-benzo(d)azepin-3-yl-methyl)-aniline

25 (103) 4-(7-methoxy-2,3,4,5-tetrahydro-benzo(d)azepin-3-yl-methyl)-aniline

(104) 4-(7-methyl-2,3,4,5-tetrahydro-benzo(d)azepin-3-yl-methyl)-aniline

(105) 4-(7,8-dimethoxy-2,3,4,5-tetrahydro-benzo(d)azepin-3-yl-methyl)-aniline

30

(106) 4-(6,7-dichloro-1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-aniline

(107) 4-(6,7-dimethyl-1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-aniline

(108) 4-(6-chloro-1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-aniline

5

(109) 4-(7-chloro-1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-aniline

(110) 4-(6-methoxy-1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-aniline

10

(111) 4-(7-methoxy-1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-aniline

(112) 4-(2,3,4,5-tetrahydro-azepino(4,5-b)pyrazin-3-yl-methyl)-aniline

(113) 4-(7-amino-2,3,4,5-tetrahydro-azepino(4,5-b)pyrazin-3-yl-methyl)-aniline

15

(114) 4-(2-amino-5,6,7,8-tetrahydro-azepino(4,5-d)thiazol-6-yl-methyl)-aniline

(115) 4-(5,6,7,8-tetrahydro-azepino(4,5-d)thiazol-6-yl-methyl)-aniline

20

(116) 4-(4-methyl-piperazin-1-yl)-aniline

(117) 4-[N-(2-dimethylamino-ethyl)-N-methyl-amino]-aniline

(118) 4-[N-(3-dimethylamino-propyl)-N-methyl-amino]-aniline

25

(119) N-(3-dimethylamino-propyl)-N-methylsulphonyl-p-phenylenediamine

(120) 4-[(N-dimethylaminocarbonylmethyl-N-methylsulphonyl)-amino]-aniline

30

(121) N-(4-aminophenyl)-N-methyl-methanesulphonamide

(122) 4-(imidazol-4-yl)-aniline

(123) 4-(tetrazol-5-yl)-aniline

5 (124) 4-[N-(2-dimethylamino-ethyl)-N-propionyl-amino]-aniline

(125) N-(dimethylaminomethylcarbonyl)-N-methyl-p-phenylenediamine

(126) N-[(2-dimethylamino-ethyl)-carbonyl]-N-methyl-p-phenylenediamine

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(127) 4-(N-acetyl-N-dimethylaminocarbonylmethyl)-amino)-aniline

(128) N-methylaminocarbonylmethyl-N-methylsulphonyl-p-phenylenediamine

15

(129) N-aminocarbonylmethyl-N-methylsulphonyl-p-phenylenediamine

(130) 4-(imidazolidin-2,4-dion-5-ylidene-methyl)-aniline

(131) 4-(imidazolidin-2,4-dion-5-yl-methyl)-aniline

20

(132) 4-(2-oxo-pyrrolidin-1-yl-methyl)-aniline

(133) N-cyanomethyl-N-methylsulphonyl-p-phenylenediamine

25

(134) 4-[2-(imidazol-4-yl)-ethyl]-aniline

(135) 4-[(4-methyl-piperazin-1-yl)-methyl]-aniline

(136) 4-[N-(2-(N-benzyl-N-methyl-amino)-ethyl)-N-methylsulphonyl-amino]-aniline

30

(137) 4-[N-(3-(N-benzyl-N-methyl-amino)-propyl)-N-methylsulphonyl-amino]-aniline

(138) N-cyclohexyl-p-phenylenediamine

(139) 4-(pyridin-4-yl-methyl)-aniline

5

(140) 4-(imidazol-1-yl-methyl)-aniline

(141) 4-benzyl-aniline

10 (142) N-(3-trifluoroacetyl-amino-propyl)-N-methylsulphonyl-p-phenylenediamine

(143) tert.butyl 4-amino-phenylacetate

(144) 4-(imidazol-2-yl)-aniline

15

(145) 4-(1-methyl-imidazol-2-yl)-aniline

(146) 4-(1-ethyl-imidazol-2-yl)-aniline

20 (147) 4-(1-benzyl-imidazol-2-yl)-aniline

(148) 4-[N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino]-3-amino-aniline

(149) 4-[N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino]-3-chloro-aniline

25

(150) 4-[N-(2-dimethylamino-ethyl)-N-acetyl-amino]-3-amino-aniline

(151) 4-[N-(2-dimethylamino-ethyl)-N-acetyl-amino]-3-bromo-aniline

30 (152) 4-[2-(4-hydroxy-piperidin-1-yl)-ethyl-amino]-aniline

(153) N-(2-dimethylamino-ethyl)-N-ethylsulphonyl-p-phenylenediamine

(154) N-(2-dimethylamino-ethyl)-N-propylsulphonyl-p-phenylenediamine

5 (155) N-(2-dimethylamino-ethyl)-N-isopropylsulphonyl-p-phenylenediamine

(156) N-(2-dimethylamino-ethyl)-N-butylsulphonyl-p-phenylenediamine

10

(157) N-(2-dimethylamino-ethyl)-N-benzylsulphonyl-p-phenylenediamine

(158) N-(2-dimethylamino-ethyl)-N-phenylsulphonyl-p-phenylenediamine

(159) 4-((3-hydroxy-pyrrolidin-1-yl)-methyl)-aniline

15

(160) 4-[N-(2-dimethylamino-ethyl)-N-(furan-2-carbonyl)-amino]-aniline

(161) 4-[N-(2-dimethylamino-ethyl)-N-(2-methoxy-benzoyl)-amino]-aniline

(162) 4-[N-(2-dimethylamino-ethyl)-N-(pyridine-3-carbonyl)-amino]-aniline

20

(163) 4-[N-(2-dimethylamino-ethyl)-N-(phenyl-acetyl)-amino]-aniline

(164) N-(piperidin-1-yl-methylcarbonyl)-N-methyl-p-phenylenediamine

25

(165) N-(morpholin-4-yl-methylcarbonyl)-N-methyl-p-phenylenediamine

(166) N-[(4-benzyl-piperazin-1-yl)-methylcarbonyl]-N-methyl-p-phenylenediamine

(167) N-(pyrrolidin-1-yl-methylcarbonyl)-N-methyl-p-phenylenediamine

30

(168) 4-(5-methyl-imidazol-4-yl)-aniline



(169) N-[(2-dimethylamino-ethyl)-carbonyl]-N-isopropyl-p-phenylenediamine

(170) N-[(2-dimethylamino-ethyl)-carbonyl]-N-benzyl-p-phenylenediamine

5

(171) N-(N-aminocarbonylmethyl-N-methyl-amino)-methylcarbonyl)-N-methyl-p-phenylenediamine

(172) N-[(N-benzyl-N-methyl-amino)-methylcarbonyl]-N-methyl-p-phenylenediamine

10

(173) N-[di-(2-methoxyethyl)-amino-methylcarbonyl]-N-methyl-p-phenylenediamine

(174) N-[(2-(4-tert.butoxycarbonyl-piperazin-1-yl)-ethyl)-carbonyl]-N-methyl-p-phenylenediamine

15

(175) N-[(2-(piperidin-1-yl)-ethyl)-carbonyl]-N-methyl-p-phenylenediamine

(176) N-[(2-(N-benzyl-N-methyl-amino)-ethyl)-carbonyl]-N-methyl-p-phenylenediamine

20

(177) N-(dimethylaminomethylcarbonyl)-N-isopropyl-p-phenylenediamine

(178) N-(piperidin-1-yl-methylcarbonyl)-N-isopropyl-p-phenylenediamine

(179) N-[(4-tert.butoxycarbonyl-piperazin-1-yl)-methylcarbonyl]-N-isopropyl-p-phenylenediamine

25

(180) N-[(N-benzyl-N-methyl-amino)-methylcarbonyl]-N-benzyl-p-phenylenediamine

(181) N-(dimethylaminomethylcarbonyl)-N-benzyl-p-phenylenediamine

30

(182) N-(piperidin-1-yl-methylcarbonyl)-N-benzyl-p-phenylenediamine

(183) 4-(1,2,4-triazol-1-yl-methyl)-aniline

(184) 4-(1,2,3-triazol-2-yl-methyl)-aniline

5

(185) 4-(1,2,3-triazol-1-yl-methyl)-aniline

(186) 4-[(N-ethoxycarbonylmethyl-N-methyl-amino)-methyl]-aniline

10

(187) 4-[(N-aminocarbonylmethyl-N-methyl-amino)-methyl]-aniline

(188) 4-(azetidin-1-yl-methyl)-aniline

(189) 4-[(di-(2-methoxy-ethyl)-amino)-methyl]-aniline

15

(190) 4-[(N-(2-(2-methoxy-ethoxy)-ethyl)-N-methyl-amino)-methyl]-aniline

(191) 4-[N-(N-tert.butoxycarbonyl-3-amino-propyl)-N-methyl-aminomethyl]-aniline

20

(192) 4-[(N-(methylcarbamoyl-methyl)-N-methyl-amino)-methyl]-aniline

(193) 4-[(N-(dimethylcarbamoyl-methyl)-N-methyl-amino)-methyl]-aniline

(194) 4-[(N-propyl-N-methyl-amino)-methyl]-aniline

25

(195) 4-[(N-(2-dimethylamino-ethyl)-N-methyl-amino)-methyl]-aniline

(196) 4-[(N-(3-dimethylamino-propyl)-N-methyl-amino)-methyl]-aniline

30

(197) 4-[(N-(2-methoxy-ethyl)-N-methyl-amino)-methyl]-aniline

(198) 4-[(N-(2-hydroxy-ethyl)-N-methyl-amino)-methyl]-aniline

(199) 4-[(N-(dioxolan-2-yl-methyl)-N-methyl-amino)-methyl]-aniline

5 (200) 4-(3-oxo-piperazin-1-yl-methyl)-aniline

(201) N-[di-(2-hydroxyethyl)-amino-methylcarbonyl]-N-methyl-p-phenylenediamine

(202) N-[(N-(2-methoxyethyl)-N-methyl-amino)-methylcarbonyl]-N-methyl-p-  
10 phenylenediamine

(203) N-[(N-(2-dimethylamino-ethyl)-N-methyl-amino)-methylcarbonyl]-N-methyl-p-  
phenylenediamine

15 (204) N-[(4-methyl-piperazin-1-yl)-methylcarbonyl]-N-methyl-p-phenylenediamine

(205) N-[(imidazol-1-yl)-methylcarbonyl]-N-methyl-p-phenylenediamine

(206) N-[(phthalimido-2-yl)-methylcarbonyl]-N-methyl-p-phenylenediamine  
20

#### Example XXI

4-(4-hydroxymethyl-piperidin-1-yl-methyl-amino)-aniline

---

25 1.1 g of 4-(4-ethoxycarbonyl-piperidin-1-yl-methyl-amino)-aniline are suspended in 15 ml of tetrahydrofuran. 175 mg of lithium borohydride are added at room temperature, stirred for 24 h, another 175 mg of lithium borohydride are added and after a further 7.5 hours 15 ml of water are added and the mixture is stirred for 10 minutes. It is extracted three times with 15 ml of ethyl acetate. The combined organic phases are washed with water and  
30 saturated saline solution, dried over sodium sulphate and concentrated by rotary

evaporation. The residue is purified over a silica gel column with methylene chloride/methanol/ammonia 4:1:0.01 as eluant.

Yield: 200 mg (27 % of theory)

R<sub>f</sub> value: 0.4 (silica gel, methylene chloride/methanol/ammonia 4:1:0.01)

5 Melting point: 157°C

### Example XXII

methyl 4-methoxycarbonylmethyl-3-nitro-benzoate

---

10

54.3 g of methyl 3-nitro-benzoate and 29.0 g of methyl chloroacetate are dissolved in 100 ml of dimethylformamide and this solution is added dropwise at -10°C to a solution of 78.5 g of potassium-tert. butoxide in 500 ml of dimethylformamide. The mixture is stirred for another 10 minutes at room temperature and after this time the solution is poured onto 350

15

ml of concentrated hydrochloric acid in 2 l of ice water. The solution is stirred for 0.5 hours, the precipitate obtained is suction filtered and washed with water. The product is recrystallised from 150 ml of methanol and dried at 40°C *in vacuo*.

Yield: 48.3 g of (51 % of theory), contains about 20 % of methyl 6-methoxycarbonylmethyl-3-nitro-benzoate

20

R<sub>f</sub> value: 0.7 (silica gel, petroleum ether/ethyl acetate = 1:1)

Melting point: 65-73 °C

The following compound is prepared analogously to Example XXII:

25

(1) ethyl 4-methoxycarbonylmethyl-3-nitro-benzoate

Prepared from ethyl 4-thoxycarbonylmethyl-3-nitro-benzoate

Example XXIII

methyl 2-indolinone-6-carboxylate

---

5 48.3 g of methyl 4-methoxycarbonylmethyl-3-nitro-benzoate are dissolved in 800 ml of concentrated acetic acid, 5.0 g of palladium on carbon (10%) are added and the solution is hydrogenated for 2.5 hours at room temperature and 50 psi. The catalyst is filtered off and the filtrate is evaporated down. The residue is taken up in 150 ml of tert.-butylmethyl ether, filtered again and dried *in vacuo* at 100°C.

10 Yield: 28.6 g (98 % of theory),

R<sub>f</sub> value: 0.4 (silica gel, methylene chloride/methanol = 10:1)

Melting point: 208-211 °C

The following compound is prepared analogously to Example XXIII:

15

(1) ethyl 2-indolinone-6-carboxylate

Prepared from ethyl 4-methoxycarbonylmethyl-3-nitro-benzoate

Example XXIV

20

1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone

---

15.0 g of ethyl 2-indolinone-6-carboxylate, 49.6 ml of triethyl orthobenzoate and 150 ml of acetic anhydride are stirred for 4 hours at 110°C. After this time the solvent is removed, the  
25 residue is recrystallised from petroleum ether and dried *in vacuo* at 50°C.

Yield: 16.9 g (61 % of theory),

R<sub>f</sub> value: 0.5 (silica gel, petroleum ether/methylene chloride/ethyl acetate = 5:4:1)

Melting point: 98-100°C

C<sub>22</sub>H<sub>21</sub>NO<sub>5</sub>

30

The following compounds are prepared analogously to Example XXIV:

(1) 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone

Prepared from methyl 2-indolinone-6-carboxylate, triethyl orthobenzoate and acetic anhydride

5

(2) 1-acetyl-3-(1-ethoxy-1-ethyl-methylene)-6-ethoxycarbonyl-2-indolinone

Prepared from ethyl 2-indolinone-6-carboxylate, triethyl orthopropionate and acetic anhydride

10 Preparation of the final compounds:

#### Example 1

15 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

---

300 mg of resin obtained according to Example II are suspended in 3 ml of dimethylformamide and shaken with 0.2 g of 4-(piperidin-1-yl-methyl)-aniline for 22 hours at 70°C. Then it is filtered off and the resin is washed several times with methylene chloride, methanol and dimethylformamide. Then 1 ml of methanolic ammonia is added for 2 hours in order to eliminate the acetyl group. Then after further washing 4 ml of 10% trifluoroacetic acid in methylene chloride are added during another 60 minutes, the resin is separated off and the solution is evaporated down.

Yield: 69 mg

25  $R_f$  value: 0.1 (silica gel, methylene chloride/methanol = 9:1)

$C_{28}H_{28}N_4O_2$

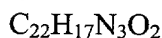
Mass spectrum:  $m/z = 452 (m^+)$

The following compounds are prepared analogously to Example 1:

30

(1) 3-Z-(1-Anilino-1-phenyl-methylene)-6-carbamoyl-2-indolinone

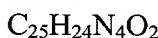
Prepared from the resin obtained according to Example II and aniline



Mass spectrum:  $m/z = 355$  ( $m^+$ )

- 5 (2) 3-Z-[1-(4-dimethylaminomethyl-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 4-dimethylaminomethyl-aniline

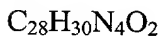


- 10 Mass spectrum:  $m/z = 412$  ( $m^+$ )

- (3) 3-Z-[1-(4-(2-diethylamino-ethyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 4-(2-diethylamino-ethyl)-aniline

15

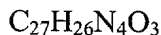


Mass spectrum:  $m/z = 454$  ( $m^+$ )

- 20 (4) 3-Z-[1-(4-(morpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 4-(morpholin-4-yl-methyl)-aniline

$R_f$  value: 0.50 (silica gel, methylene chloride/methanol = 4:1)



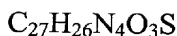
- 25 Mass spectrum:  $m/z = 454$  ( $m^+$ )

- (5) 3-Z-[1-(4-(1-oxo-thiomorpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 4-(1-oxo-thiomorpholin-4-yl-methyl)-aniline

30

$R_f$  value: 0.30 (silica gel, methylene chloride/methanol = 9:1)

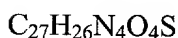


Mass spectrum:  $m/z = 486$  ( $m^+$ )

- 5 (6) 3-Z-[1-(4-(1,1-dioxo-thiomorpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 4-(1,1-dioxo-thiomorpholin-4-yl-methyl)-aniline

$R_f$  value: 0.30 (silica gel, methylene chloride/methanol = 9:1)

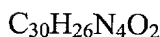


- 10 Mass spectrum:  $m/z = 502$  ( $m^+$ )

- (7) 3-Z-[1-(4-(benzylaminomethyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

- 15 Prepared from the resin obtained according to Example II and 4-[N-(phenyl-methyl)-N-tert.butoxycarbonyl-aminomethyl]-aniline

$R_f$  value: 0.40 (silica gel, methylene chloride/methanol = 4:1)



Mass spectrum:  $m/z = 474$  ( $m^+$ )

- 20 (8) 3-Z-[1-(4-(amino-methyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 4-(N-tert.butoxycarbonyl-aminomethyl)-aniline

$R_f$  value: 0.10 (silica gel, methylene chloride/methanol = 4:1)

- 25  $\text{C}_{23}\text{H}_{20}\text{N}_4\text{O}_2$

Mass spectrum:  $m/z = 384$  ( $m^+$ )

- (9) 3-Z-[1-(4-(2,6-dimethylpiperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

- 30 Prepared from the resin obtained according to Example II and 4-(2,6-dimethylpiperidin-1-yl-methyl)-aniline



R<sub>f</sub> value: 0.45 (silica gel, methylene chloride/methanol = 4:1)

C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>2</sub>

Mass spectrum: m/z = 480 (m<sup>+</sup>)

- 5 (10) 3-Z-[1-(4-(pyrrolidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 4-(pyrrolidin-1-yl-methyl)-aniline

R<sub>f</sub> value: 0.15 (silica gel, methylene chloride/methanol = 4:1)

- 10 C<sub>27</sub>H<sub>26</sub>N<sub>4</sub>O<sub>2</sub>

Mass spectrum: m/z = 438 (m<sup>+</sup>)

- (11) 3-Z-[1-(3-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

- 15 Prepared from the resin obtained according to Example II and 3-dimethylaminomethyl-aniline

R<sub>f</sub> value: 0.23 (silica gel, methylene chloride/methanol = 4:1)

C<sub>25</sub>H<sub>24</sub>N<sub>4</sub>O<sub>2</sub>

Mass spectrum: m/z = 412 (m<sup>+</sup>)

- 20

- (12) 3-Z-[1-(3-(N-methyl-N-ethyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 3-(N-methyl-N-ethyl-aminomethyl)-aniline

- 25 R<sub>f</sub> value: 0.23 (silica gel, methylene chloride/methanol = 4:1)

C<sub>26</sub>H<sub>26</sub>N<sub>4</sub>O<sub>2</sub>

Mass spectrum: m/z = 426 (m<sup>+</sup>)

- 30 (13) 3-Z-[1-(3-(methylaminomethyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 4-(N-tert.butoxycarbonyl-N-methyl-aminomethyl)-aniline

R<sub>f</sub> value: 0.06 (silica gel, methylene chloride/methanol = 4:1)

C<sub>24</sub>H<sub>22</sub>N<sub>4</sub>O<sub>2</sub>

5 Mass spectrum: m/z = 399 (m+H<sup>+</sup>)

(14) 3-Z-[1-(3-hydroxymethyl-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II and 3-amino-benzyl alcohol

R<sub>f</sub> value: 0.7 (silica gel, methylene chloride/methanol = 4:1)

10 C<sub>23</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>

Mass spectrum: m/z = 385 (m<sup>+</sup>)

(15) 3-Z-[1-(4-(methoxycarbonylmethyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

15 Prepared from the resin obtained according to Example II and

4-(N-methoxycarbonylmethyl-N-tert.butoxycarbonyl-aminomethyl)-aniline

R<sub>f</sub> value: 0.40 (silica gel, methylene chloride/methanol = 9:1)

C<sub>26</sub>H<sub>24</sub>N<sub>4</sub>O<sub>4</sub>

Mass spectrum: m/z = 457 (m+H<sup>+</sup>)

20

(16) 3-Z-[1-(4-(N-methylsulphonyl-N-(dimethylaminocarbonyl-methyl)-amino)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II and 4-(N-methylsulphonyl-N-(dimethylaminocarbonylmethyl)-amino)-aniline

25 R<sub>f</sub> value: 0.40 (silica gel, methylene chloride/methanol = 9:1)

C<sub>27</sub>H<sub>27</sub>N<sub>5</sub>O<sub>5</sub>S

Mass spectrum: m/z = 533 (m<sup>+</sup>)

(17) 3-Z-[1-(4-(N-acetyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

30

Prepared from the resin obtained according to Example II and 4-(N-acetyl-aminomethyl)-aniline

R<sub>f</sub> value: 0.70 (silica gel, methylene chloride/methanol = 4:1)

C<sub>25</sub>H<sub>22</sub>N<sub>4</sub>O<sub>3</sub>

5 Mass spectrum: m/z = 426 (m<sup>+</sup>)

(18) 3-Z-[1-(3,4-dimethoxy-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II and 3,4-dimethoxy-aniline

R<sub>f</sub> value: 0.40 (silica gel, methylene chloride/methanol = 9:1)

10 C<sub>24</sub>H<sub>21</sub>N<sub>3</sub>O<sub>4</sub>

Mass spectrum: m/z = 415 (m<sup>+</sup>)

(19) 3-Z-[1-(4-(morpholin-4-yl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

15 Prepared from the resin obtained according to Example II and 4-morpholin-4-yl-aniline

R<sub>f</sub> value: 0.20 (silica gel, methylene chloride/methanol = 9:1)

C<sub>26</sub>H<sub>24</sub>N<sub>4</sub>O<sub>3</sub>

Mass spectrum: m/z = 440 (m<sup>+</sup>)

20 (20) 3-Z-[1-(4-acetylamino-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II and 4-acetylamino-aniline

R<sub>f</sub> value: 0.25 (silica gel, methylene chloride/methanol = 9:1)

C<sub>24</sub>H<sub>20</sub>N<sub>4</sub>O<sub>3</sub>

Mass spectrum: m/z = 412 (m<sup>+</sup>)

25

(21) 3-Z-[1-(4-amino-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II and 4-amino-aniline

R<sub>f</sub> value: 0.40 (silica gel, methylene chloride/methanol = 9:1)

C<sub>22</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub>

30 Mass spectrum: m/z = 370 (m<sup>+</sup>)

(22) 3-Z-[1-(4-N-methyl-N-acetyl-amino-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II and 4-(N-methyl-N-acetyl-amino)-aniline

5  $C_{25}H_{22}N_4O_3$

Mass spectrum:  $m/z = 426 (m^+)$

(23) 3-Z-[1-(4-ethoxycarbonyl-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II and ethyl 4-amino-benzoate

10  $C_{25}H_{21}N_3O_4$

Mass spectrum:  $m/z = 427 (m^+)$

(24) 3-Z-[1-(4-carboxy-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II and 4-amino-benzoic acid

15  $R_f$  value: 0.11 (silica gel, methylene chloride/methanol = 9:1)

$C_{23}H_{17}N_3O_4$

Mass spectrum:  $m/z = 398 (m-H^+)$

(25) 3-Z-[1-(4-benzylcarbamoyl-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

20 Prepared from the resin obtained according to Example II and 4-amino-benzoic acid-benzylamide

$R_f$  value: 0.21 (silica gel, methylene chloride/methanol = 9:1)

$C_{30}H_{24}N_4O_3$

Mass spectrum:  $m/z = 488 (m^+)$

25

(26) 3-Z-[1-(cyclohexyl-amino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II and cyclohexylamine

$R_f$  value: 0.60 (silica gel, methylene chloride/methanol = 9:1)

$C_{22}H_{23}N_3O_2$

30 Mass spectrum:  $m/z = 361 (m^+)$

(27) 3-Z-[1-(4-amino-cyclohexyl-amino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 4-amino-cyclohexylamine

$C_{22}H_{24}N_4O_2$

5 Mass spectrum:  $m/z = 376 (m^+)$

(28) 3-Z-[1-(N-methyl-piperidine-4-yl-amino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 4-amino-1-methyl-

10 piperidine

$R_f$  value: 0.15 (silica gel, methylene chloride/methanol = 4:1)

$C_{22}H_{24}N_4O_2$

Mass spectrum:  $m/z = 376 (m^+)$

15 (29) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II(2) and 4-(piperidin-1-yl-methyl)-aniline

$R_f$  value: 0.30 (silica gel, methylene chloride/methanol = 4:1)

20  $C_{23}H_{26}N_4O_2$

Mass spectrum:  $m/z = 390 (m^+)$

(30) 3-Z-[1-(3-dimethylaminomethyl-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

25 Prepared from the resin obtained according to Example II(2) and 3-dimethylaminomethyl-aniline

$R_f$  value: 0.51 (silica gel, methylene chloride/methanol = 4:1)

$C_{20}H_{22}N_4O_2$

Mass spectrum:  $m/z = 351 (m+H^+)$

30

(31) 3-Z-[1-(4-(N-methyl-N-benzyl-aminomethyl)-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II(2) and 4-(N-methyl-N-benzyl-aminomethyl)-aniline

5  $R_f$  value: 0.73 (silica gel, methylene chloride/methanol = 4:1)

$C_{26}H_{26}N_4O_2$

Mass spectrum:  $m/z = 426 (m^+)$

(32) 3-Z-[1-(4-(N-methylsulphonyl-N-(2-dimethylamino-ethyl)-amino)-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

10

Prepared from the resin obtained according to Example II(2) and 4-(N-methylsulphonyl-N-(2-dimethylamino-ethyl)-amino)-aniline

$C_{22}H_{27}N_5O_4S$

Mass spectrum:  $m/z = 458 (m+H^+)$

15

(33) 3-Z-[1-(4-chloro-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II(2) and 4-chloro-aniline

$R_f$  value: 0.10 (silica gel, methylene chloride/methanol = 9:1)

$C_{17}H_{14}ClN_3O_2$

20 Mass spectrum:  $m/z = 327/329 (m^+)$

(34) 3-Z-[1-(3-chloro-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II(2) and 3-chloro-aniline

$R_f$  value: 0.11 (silica gel, methylene chloride/methanol = 9:1)

25  $C_{17}H_{14}ClN_3O_2$

Mass spectrum:  $m/z = 327/329 (m^+)$

(35) 3-Z-[1-(4-methoxycarbonyl-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II(2) and methyl 4-amino-benzoate

30  $R_f$  value: 0.11 (silica gel, methylene chloride/methanol = 9:1)

$C_{19}H_{17}N_3O_4$

Mass spectrum:  $m/z = 351$  ( $m^+$ )

(36) 3-Z-[1-(4-carboxy-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II(2) and 4-amino-benzoic acid

5  $C_{18}H_{15}N_3O_4$

Mass spectrum:  $m/z = 336$  ( $m-H^+$ )

(37) 3-Z-[1-(4-methyl-3-nitro-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II(2) and 4-methyl-3-nitro-aniline

10  $R_f$  value: 0.82 (silica gel, methylene chloride/methanol = 4:1)

$C_{18}H_{16}N_4O_4$

Mass spectrum:  $m/z = 352$  ( $m^+$ )

(38) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-propyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

15

Prepared from the resin obtained according to Example II(4) and 4-(piperidin-1-yl-methyl)-aniline

$R_f$  value: 0.37 (silica gel, methylene chloride/methanol = 4:1)

$C_{25}H_{30}N_4O_2$

20 Mass spectrum:  $m/z = 418$  ( $m^+$ )

(39) 3-Z-[1-(3-dimethylaminomethyl-anilino)-1-propyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II(4) and 3-dimethylaminomethyl-aniline

25

$R_f$  value: 0.42 (silica gel, methylene chloride/methanol = 4:1)

$C_{22}H_{26}N_4O_2$

Mass spectrum:  $m/z = 378$  ( $m^+$ )

30 (40) 3-Z-[1-(4-(N-methyl-N-benzyl-aminomethyl)-anilino)-1-propyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II(4) and 4-(N-methyl-N-benzyl-aminomethyl)-aniline

R<sub>f</sub> value: 0.81 (silica gel, methylene chloride/methanol = 4:1)

C<sub>28</sub>H<sub>30</sub>N<sub>4</sub>O<sub>2</sub>

5 Mass spectrum: m/z = 454 (m<sup>+</sup>)

(41) 3-Z-[1-(4-(N-methylsulphonyl-N-(2-dimethylamino-ethyl)-amino)-anilino)-1-propyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II(4) and 4-(N-methylsulphonyl-N-(2-dimethylamino-ethyl)-amino)-aniline

R<sub>f</sub> value: 0.59 (silica gel, methylene chloride/methanol = 4:1)

C<sub>24</sub>H<sub>31</sub>N<sub>5</sub>O<sub>4</sub>S

Mass spectrum: m/z = 486 (m+H<sup>+</sup>)

15 (42) 3-Z-[1-(4-chloro-anilino)-1-propyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II(4) and 4-chloro-aniline

R<sub>f</sub> value: 0.17 (silica gel, methylene chloride/methanol = 9:1)

C<sub>19</sub>H<sub>18</sub>ClN<sub>3</sub>O<sub>2</sub>

Mass spectrum: m/z = 355/357 (m<sup>+</sup>)

20 (43) 3-Z-[1-(3-chloro-anilino)-1-propyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II(4) and 3-chloro-aniline

R<sub>f</sub> value: 0.12 (silica gel, methylene chloride/methanol = 9:1)

C<sub>19</sub>H<sub>18</sub>ClN<sub>3</sub>O<sub>2</sub>

25 Mass spectrum: m/z = 355/357 (m<sup>+</sup>)

(44) 3-Z-[1-(4-methoxycarbonyl-anilino)-1-propyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II(4) and methyl 4-amino-benzoate

R<sub>f</sub> value: 0.8 (silica gel, methylene chloride/methanol = 4:1)

30 C<sub>21</sub>H<sub>21</sub>N<sub>3</sub>O<sub>4</sub>

Mass spectrum: m/z = 379 (m<sup>+</sup>)



(45) 3-Z-[1-(4-carboxy-anilino)-1-propyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II(4) and 4-amino-benzoic acid

$C_{20}H_{19}N_3O_4$

5 Mass spectrum:  $m/z = 364 (m-H^+)$

(46) 3-Z-[1-(4-methyl-3-nitro-anilino)-1-propyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II(4) and 4-methyl-3-nitro-aniline

$R_f$  value: 0.86 (silica gel, methylene chloride/methanol = 4:1)

10  $C_{20}H_{20}N_4O_4$

Mass spectrum:  $m/z = 380 (m^+)$

### Example 2

15 3-Z-[1-(3-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

---

2.0 g of resin obtained according to Example II are reacted analogously to Example 1 with 2.0 g of 3-aminobenzyl alcohol in 20 ml of dimethylformamide for 22 hours at 70° C. Then

20 the solvent is suction filtered and the resin is washed several times with dimethylformamide and methylene chloride. Then 200 mg of the moist charged resin are suspended in 2 ml of methylene chloride and left to stand with 0.2 ml of methanesulphonic acid chloride and 0.1 ml of triethylamine for 2 hours at room temperature. Then the resin is washed several times with methylene chloride, suspended in 2 ml of methylene chloride  
25 and combined with 0.2 ml of piperidine. After 1 hour the resin is washed with methylene chloride and dimethylformamide and then treated with trifluoroacetic acid analogously to Example 1.

Yield: 15 mg

$R_f$  value: 0.30 (silica gel, methylene chloride/methanol = 4:1)

30  $C_{28}H_{28}N_4O_2$

Mass spectrum:  $m/z = 452 (m^+)$

The following compounds are prepared analogously to Example 2:

(1) 3-Z-[1-(3-(diethylaminomethyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and diethylamine

R<sub>f</sub> value: 0.80 (silica gel, methylene chloride/methanol = 4:1)

C<sub>27</sub>H<sub>28</sub>N<sub>4</sub>O<sub>2</sub>

Mass spectrum: m/z = 440 (m<sup>+</sup>)

(2) 3-Z-[1-(3-(benzylaminomethyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and benzylamine

R<sub>f</sub> value: 0.80 (silica gel, methylene chloride/methanol = 4:1)

C<sub>30</sub>H<sub>26</sub>N<sub>4</sub>O<sub>2</sub>

Mass spectrum: m/z = 474 (m<sup>+</sup>)

(3) 3-Z-[1-(3-(N-methyl-N-benzyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and N-methyl-benzylamine

R<sub>f</sub> value: 0.80 (silica gel, methylene chloride/methanol = 4:1)

C<sub>31</sub>H<sub>28</sub>N<sub>4</sub>O<sub>2</sub>

Mass spectrum: m/z = 488 (m<sup>+</sup>)

(4) 3-Z-[1-(3-(butylaminomethyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and butylamine

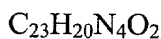
R<sub>f</sub> value: 0.40 (silica gel, methylene chloride/methanol = 4:1)

C<sub>27</sub>H<sub>28</sub>N<sub>4</sub>O<sub>2</sub>

Mass spectrum: m/z = 440 (m<sup>+</sup>)

(5) 3-Z-[1-(3-(aminomethyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and ammonia

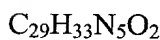


5 Mass spectrum:  $m/z = 385$  ( $m+H^+$ )

(6) 3-Z-[1-(3-(N-(3-dimethylaminopropyl)-N-methyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 1-dimethylamino-3-methylaminopropane

$R_f$  value: 0.67 (silica gel, methylene chloride/methanol = 4:1)

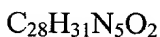


Mass spectrum:  $m/z = 484$  ( $m+H^+$ )

(7) 3-Z-[1-(3-(N-(2-dimethylaminoethyl)-N-methyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 1-dimethylamino-2-methylaminoethane

$R_f$  value: 0.40 (silica gel, methylene chloride/methanol = 4:1)



Mass spectrum:  $m/z = 470$  ( $m+H^+$ )

Example 3

3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

---

5

1.5 g of 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 1.1 g of 4-(piperidin-1-yl-methyl)-aniline are dissolved in 15 ml of dimethylformamide and stirred for 45 minutes at 100°C. After cooling 5.0 ml of piperidine are added and the mixture is stirred for another 3 hours at room temperature. The solvent is removed and the residue purified over an aluminium oxide column (activity: 2-3) with methylene chloride/ethanol (100:3) as eluant.

10

Yield: 1.1 g (58% of theory),

R<sub>f</sub> value: 0.5 (aluminium oxide, methylene chloride/ethanol = 100:3)

C<sub>30</sub>H<sub>31</sub>N<sub>3</sub>O<sub>3</sub>

15

Mass spectrum: m/z = 481 [M<sup>+</sup>]

The following compounds are prepared analogously to Example 3:

(1) 3-Z-[1-(4-bromo-anilino)-1-phenyl-methylene]-6-ethoxy-carbonyl-2-indolinone

20

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-bromoaniline

R<sub>f</sub> value: 0.4 (silica gel, toluene/ethyl acetate = 5:1)

C<sub>24</sub>H<sub>19</sub>BrN<sub>2</sub>O<sub>3</sub>

Mass spectrum: m/z = 462/464 [M<sup>+</sup>]

25

(2) 3-Z-[1-(3-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 3-(dimethylaminomethyl)-aniline

30

R<sub>f</sub> value: 0.5 (aluminium oxide, methylene chloride/ethanol = 30:1)

C<sub>27</sub>H<sub>27</sub>N<sub>3</sub>O<sub>3</sub>

ESI mass spectrum:  $m/z = 442$   $[M+H]^+$

(3) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

5 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-(dimethylaminomethyl)-aniline

$R_f$  value: 0.7 (aluminium oxide, ethyl acetate/ethanol = 20:1)

$C_{27}H_{27}N_3O_3$

ESI mass spectrum:  $m/z = 442$   $[M+H]^+$

10

(4) 3-Z-[1-(4-[(2,6-dimethyl-piperidin-1-yl)-methyl]-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-[(2,6-dimethyl-piperidin-1-yl)-methyl]-aniline

15  $R_f$  value: 0.6 (silica gel, methylene chloride/ethanol = 5:1)

$C_{32}H_{35}N_3O_3$

Mass spectrum:  $m/z = 509$   $[M]^+$

(5) 3-Z-[1-(4-(2-dimethylamino-ethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

20

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-(2-dimethylamino-ethyl)-aniline

$R_f$  value: 0.2 (silica gel, methylene chloride/ethanol = 5:1)

$C_{28}H_{29}N_3O_3$

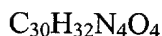
25 Mass spectrum:  $m/z = 455$   $[M]^+$

(6) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-aniline

30

$R_f$  value: 0.4 (aluminium oxide, methylene chloride/ethanol = 20:1)

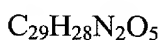


Mass spectrum:  $m/z = 512 [M^+]$

- 5 (7) 3-Z-[1-(4-tert.butyloxycarbonyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-tert.butyloxycarbonyl-aniline

$R_f$  value: 0.4 (aluminium oxide, methylene chloride/ethanol = 40:1)

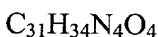


- 10 Mass spectrum:  $m/z = 484 [M^+]$

- (8) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

- 15 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-aniline

$R_f$  value: 0.2 (aluminium oxide, methylene chloride/ethanol = 40:1)



Mass spectrum:  $m/z = 526 [M^+]$

- 20 (9) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and N-(2-dimethylamino-ethyl)-N-methylsulphonyl-p-phenylenediamine

$R_f$  value: 0.3 (aluminium oxide, methylene chloride/ethanol = 40:1)

- 25  $C_{29}H_{32}N_4O_5S$

Mass spectrum:  $m/z = 548 [M^+]$

- (10) 3-Z-[1-(4-(4-methyl-piperazin-1-yl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

- 30 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-(4-methyl-piperazin-1-yl)-aniline

R<sub>f</sub> value: 0.3 (aluminium oxide, ethyl acetate)

C<sub>29</sub>H<sub>30</sub>N<sub>4</sub>O<sub>3</sub>

ESI mass spectrum: m/z = 483 [M+H<sup>+</sup>]

- 5 (11) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-(N-(2-dimethylamino-ethyl)-N-methyl-amino)-aniline

R<sub>f</sub> value: 0.5 (aluminium oxide, methylene chloride/ethanol = 20:1)

- 10 C<sub>29</sub>H<sub>32</sub>N<sub>4</sub>O<sub>3</sub>

ESI mass spectrum: m/z = 485 [M+H<sup>+</sup>]

- (12) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

- 15 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-(N-(3-dimethylamino-propyl)-N-methyl-amino)-aniline

R<sub>f</sub> value: 0.5 (aluminium oxide, ethyl acetate)

C<sub>30</sub>H<sub>34</sub>N<sub>4</sub>O<sub>3</sub>

ESI mass spectrum: m/z = 499 [M+H<sup>+</sup>]

20

- (13) 3-Z-[1-(4-(N-methyl-acetylamino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-amino-N-methyl-acetanilide

- 25 R<sub>f</sub> value: 0.3 (silica gel, methylene chloride/ethanol = 15:1)

C<sub>27</sub>H<sub>25</sub>N<sub>3</sub>O<sub>4</sub>

Mass spectrum: m/z = 455 [M<sup>+</sup>]

- (14) 3-Z-[1-(4-(N-methyl-methylsulphonylamino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
- 30

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and N-(4-aminophenyl)-N-methyl-methanesulphonamide

R<sub>f</sub> value: 0.8 (aluminium oxide, ethyl acetate)

C<sub>26</sub>H<sub>25</sub>N<sub>3</sub>O<sub>5</sub>S

5 Mass spectrum: m/z = 491 [M<sup>+</sup>]

(15) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and N-(3-dimethylamino-propyl)-N-methylsulphonyl-p-phenylenediamine

R<sub>f</sub> value: 0.6 (silica gel, methylene chloride/ethanol/ammonia = 5:2:0.01)

C<sub>30</sub>H<sub>34</sub>N<sub>4</sub>O<sub>5</sub>S

ESI mass spectrum: m/z = 563 [M+H<sup>+</sup>]

15 (16) 3-Z-[1-(4-(N-dimethylaminocarbonylmethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-(N-dimethylaminocarbonylmethyl-N-methylsulphonyl)-amino)-aniline

R<sub>f</sub> value: 0.6 (silica gel, methylene chloride/ethanol = 10:1)

20 C<sub>29</sub>H<sub>30</sub>N<sub>4</sub>O<sub>6</sub>S

ESI mass spectrum: m/z = 561 [M-H<sup>-</sup>]

(17) 3-Z-[1-(4-(imidazol-4-yl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

25 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-(imidazol-4-yl)-aniline

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/ethanol/ammonia = 10:1:0.01)

C<sub>27</sub>H<sub>22</sub>N<sub>4</sub>O<sub>3</sub>

Mass spectrum: m/z = 450 [M<sup>+</sup>]

30



(18) 3-Z-[1-(4-(tetrazol-5-yl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-(tetrazol-5-yl)-aniline

5  $R_f$  value: 0.5 (silica gel, methylene chloride/ethanol = 5:1)

$C_{25}H_{20}N_6O_3$

ESI mass spectrum:  $m/z = 451 [M-H^-]$

(19) 3-Z-[1-(4-(N-benzyl-N-methyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-(N-benzyl-N-methyl-aminomethyl)-aniline

$R_f$  value: 0.4 (silica gel, methylene chloride/ethanol = 10:1)

$C_{33}H_{31}N_3O_3$

15 ESI mass spectrum:  $m/z = 516 [M-H^-]$

(20) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-propionyl-amino)-aniline)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-[N-(2-dimethylamino-ethyl)-N-propionyl-amino]-aniline

$R_f$  value: 0.2 (silica gel, methylene chloride/ethanol = 5:1)

$C_{31}H_{34}N_4O_4$

ESI mass spectrum:  $m/z = 525 [M-H^-]$

(21) 3-Z-[1-(4-(pyrrolidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-(pyrrolidin-1-yl-methyl)-aniline

$R_f$  value: 0.1 (silica gel, methylene chloride/ethanol = 5:1)

30  $C_{29}H_{29}N_3O_3$

ESI mass spectrum:  $m/z = 466 [M-H^-]$

(22) 3-Z-[1-(4-(N-methyl-N-phenethyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone  
5 and 4-(N-phenethyl-N-methyl-aminomethyl)-aniline

R<sub>f</sub> value: 0.4 (silica gel, methylene chloride/ethanol = 10:1)

C<sub>34</sub>H<sub>33</sub>N<sub>3</sub>O<sub>3</sub>

ESI mass spectrum: m/z = 530 [M-H]

10 (23) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone  
and N-dimethylaminomethylcarbonyl-N-methyl-p-phenylenediamine

R<sub>f</sub> value: 0.1 (silica gel, methylene chloride/ethanol = 10:1)

15 C<sub>29</sub>H<sub>30</sub>N<sub>4</sub>O<sub>4</sub>

ESI mass spectrum: m/z = 497 [M-H]

(24) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-ethylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

20 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone  
and N-(2-dimethylamino-ethyl)-N-ethylsulphonyl-p-phenylenediamine

R<sub>f</sub> value: 0.6 (silica gel, methylene chloride/ethanol = 5:1)

C<sub>30</sub>H<sub>34</sub>N<sub>4</sub>O<sub>5</sub>S

ESI mass spectrum: m/z = 561 [M-H]

25

(25) 3-Z-[1-(4-(N-tert.butoxycarbonyl-N-ethyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone  
and 4-(N-tert.butoxycarbonyl-N-ethyl-aminomethyl)-aniline

30 R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 10:1)

C<sub>32</sub>H<sub>35</sub>N<sub>3</sub>O<sub>5</sub>

ESI mass spectrum:  $m/z = 540$   $[M-H^-]$

(26) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-ethyl-methylene]-6-ethoxycarbonyl-2-indolinone

5 Prepared from 1-acetyl-3-(1-ethoxy-1-ethyl-methylene)-6-ethoxycarbonyl-2-indolinone and 4-(piperidin-1-yl-methyl)-aniline

$R_f$  value: 0.9 (silica gel, methylene chloride/ethanol = 5:1)

$C_{26}H_{31}N_3O_3$

ESI mass spectrum:  $m/z = 432$   $[M-H^-]$

10

(27) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-ethyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-ethyl-methylene)-6-ethoxycarbonyl-2-indolinone and N-(2-dimethylamino-ethyl)-N-methylsulphonyl-p-phenylenediamine

15  $R_f$  value: 0.3 (silica gel, methylene chloride/ethanol = 5:1)

$C_{25}H_{32}N_4O_5S$

ESI mass spectrum:  $m/z = 499$   $[M-H^-]$

(28) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

20

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(dimethylaminomethyl)-aniline

$R_f$  value: 0.6 (silica gel, methylene chloride/methanol = 5:1)

$C_{26}H_{25}N_3O_3$

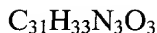
25 ESI mass spectrum:  $m/z = 428$   $[M+H^+]$

(29) 3-Z-[1-(4-[(2,6-dimethyl-piperidin-1-yl)-methyl]-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-[(2,6-dimethyl-piperidin-1-yl)-methyl]-aniline

30

$R_f$  value: 0.5 (RP 8, methanol/five percent saline solution = 4:1)

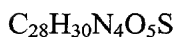


ESI mass spectrum:  $m/z = 496 [M+H^+]$

(30) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(2-dimethylamino-ethyl)-N-methylsulphonyl-p-phenylenediamine

$R_f$  value: 0.6 (silica gel, methylene chloride/methanol = 5:1)

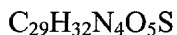


ESI mass spectrum:  $m/z = 533 [M-H^-]$

(31) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(3-dimethylamino-propyl)-N-methylsulphonyl-p-phenylenediamine

$R_f$  value: 0.5 (aluminium oxide, methylene chloride/methanol = 30:1)

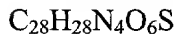


ESI mass spectrum:  $m/z = 547 [M-H^-]$

(32) 3-Z-[1-(4-(N-dimethylaminocarbonylmethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-dimethylaminocarbonylmethyl-N-methylsulphonyl)-amino)-aniline

$R_f$  value: 0.5 (aluminium oxide, methylene chloride/methanol = 20:1)



ESI mass spectrum:  $m/z = 547 [M-H^-]$

(33) 3-Z-[1-(4-(N-acetyl-N-dimethylaminocarbonylmethyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-acetyl-N-dimethylaminocarbonylmethyl)-amino)-aniline

R<sub>f</sub> value: 0.6 (silica gel, methylene chloride/methanol = 10:1)

C<sub>29</sub>H<sub>28</sub>N<sub>4</sub>O<sub>5</sub>

ESI mass spectrum: m/z = 511 [M-H]<sup>-</sup>

- 5 (34) 3-Z-[1-(4-(N-dimethylaminocarbonylmethyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-dimethylaminocarbonyl-methyl)-amino)-aniline

R<sub>f</sub> value: 0.6 (aluminium oxide, methylene chloride/methanol = 30:1)

- 10 C<sub>27</sub>H<sub>26</sub>N<sub>4</sub>O<sub>4</sub>

ESI mass spectrum: m/z = 469 [M-H]<sup>-</sup>

- (35) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

- 15 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(3-dimethylamino-propyl)-N-acetyl-p-phenylenediamine

R<sub>f</sub> value: 0.5 (aluminium oxide, methylene chloride/methanol = 20:1)

C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>4</sub>

ESI mass spectrum: m/z = 511 [M-H]<sup>-</sup>

20

- (36) 3-Z-[1-(4-(N-methylaminocarbonylmethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-methylaminocarbonylmethyl-N-methylsulphonyl-p-phenylenediamine

- 25 R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 10:1)

C<sub>27</sub>H<sub>26</sub>N<sub>4</sub>O<sub>6</sub>S

ESI mass spectrum: m/z = 533 [M-H]<sup>-</sup>

- (37) 3-Z-[1-(4-((imidazolidin-2,4-dione-5-ylidene)-methyl)-anilino)-1-phenyl-methylene]-  
30 6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((imidazolidin-2,4-dion-5-ylidene)-methyl)-aniline

R<sub>f</sub> value: 0.4 (silica gel, methylene chloride/methanol = 10:1)

C<sub>27</sub>H<sub>20</sub>N<sub>4</sub>O<sub>5</sub>

5 ESI mass spectrum: m/z = 479 [M-H<sup>-</sup>]

(38) 3-Z-[1-(4-(N-((2-dimethylamino-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-((2-dimethylamino-ethyl)-carbonyl)-N-methyl-p-phenylenediamine

R<sub>f</sub> value: 0.5 (aluminium oxide, methylene chloride/methanol = 20:1)

C<sub>29</sub>H<sub>30</sub>N<sub>4</sub>O<sub>4</sub>

ESI mass spectrum: m/z = 497 [M-H<sup>-</sup>]

15 (39) 3-Z-[1-(4-(N-tert.butoxycarbonyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-tert.butoxycarbonyl-aminomethyl)-aniline

R<sub>f</sub> value: 0.3 (aluminium oxide, methylene chloride/methanol = 20:1)

20 C<sub>29</sub>H<sub>29</sub>N<sub>3</sub>O<sub>5</sub>

ESI mass spectrum: m/z = 498 [M-H<sup>-</sup>]

(40) 3-Z-[1-(4-(2-oxo-pyrrolidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

25 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(2-oxo-pyrrolidin-1-yl-methyl)-aniline

R<sub>f</sub> value: 0.3 (silica gel, methylene chloride/methanol = 20:1)

C<sub>28</sub>H<sub>25</sub>N<sub>3</sub>O<sub>4</sub>

ESI mass spectrum: m/z = 466 [M-H<sup>-</sup>]

30

(41) 3-Z-[1-(4-(N-aminocarbonylmethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-aminocarbonylmethyl-N-methylsulphonyl-p-phenylenediamine

5  $R_f$  value: 0.7 (silica gel, methylene chloride/methanol = 5:1)

$C_{26}H_{24}N_4O_6S$

ESI mass spectrum:  $m/z = 519 [M-H^-]$

(42) 3-Z-[1-(4-(thiomorpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

10

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(thiomorpholin-4-yl-methyl)-aniline

$R_f$  value: 0.4 (silica gel, methylene chloride/methanol = 15:1)

$C_{28}H_{27}N_3O_3S$

15 ESI mass spectrum:  $m/z = 484 [M-H^-]$

(43) 3-Z-[1-(4-(1,1-dioxo-thiomorpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(1,1-dioxo-thiomorpholin-4-yl-methyl)-aniline

20

$R_f$  value: 0.5 (silica gel, methylene chloride/methanol = 10:1)

$C_{28}H_{27}N_3O_5S$

ESI mass spectrum:  $m/z = 516 [M-H^-]$

(44) 3-Z-[1-(4-(N-cyanomethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

25

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-cyanomethyl-N-methyl-sulphonyl-p-phenylenediamine

$R_f$  value: 0.6 (silica gel, methylene chloride/methanol = 10:1)

30  $C_{26}H_{22}N_4O_5S$

ESI mass spectrum:  $m/z = 501 [M-H^-]$

(45) 3-Z-[1-(4-(N-tert.butoxycarbonyl-ethylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone  
and 4-(N-ethyl-N-tert.butoxycarbonyl-aminomethyl)-aniline

R<sub>f</sub> value: 0.6 (silica gel, methylene chloride/methanol = 10:1)

C<sub>31</sub>H<sub>33</sub>N<sub>3</sub>O<sub>5</sub>

ESI mass spectrum: m/z = 526 [M-H<sup>-</sup>]

(46) 3-Z-[1-(4-(N-benzyl-N-methyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone  
and 4-(N-benzyl-N-methyl-aminomethyl)-aniline

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 10:1)

C<sub>32</sub>H<sub>29</sub>N<sub>3</sub>O<sub>3</sub>

ESI mass spectrum: m/z = 502 [M-H<sup>-</sup>]

(47) 3-Z-[1-(4-(1-oxo-thiomorpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone  
and 4-(1-oxo-thiomorpholin-4-yl-methyl)-aniline

R<sub>f</sub> value: 0.7 (silica gel, methylene chloride/methanol = 10:1)

C<sub>28</sub>H<sub>27</sub>N<sub>3</sub>O<sub>4</sub>S

ESI mass spectrum: m/z = 500 [M-H<sup>-</sup>]

(48) 3-Z-[1-(4-(2-(imidazol-4-yl)-ethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone  
and 4-(2-(imidazol-4-yl)-ethyl)-aniline

R<sub>f</sub> value: 0.4 (silica gel, methylene chloride/methanol = 5:1)

C<sub>28</sub>H<sub>24</sub>N<sub>4</sub>O<sub>3</sub>



ESI mass spectrum:  $m/z = 463$   $[M-H]^-$

(49) 3-Z-[1-(4-(morpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

- 5 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(morpholin-4-yl-methyl)-aniline

$R_f$  value: 0.5 (silica gel, methylene chloride/methanol = 10:1)

$C_{28}H_{27}N_3O_4$

ESI mass spectrum:  $m/z = 468$   $[M-H]^-$

10

(50) 3-Z-[1-(4-((4-methyl-piperazin-1-yl)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((4-methyl-piperazin-1-yl)-methyl)-aniline

- 15  $R_f$  value: 0.4 (silica gel, methylene chloride/methanol 5:1)

$C_{29}H_{30}N_4O_3$

ESI mass spectrum:  $m/z = 481$   $[M-H]^-$

(51) 3-Z-[1-(4-((2-(N-benzyl-N-methyl-amino)-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

20

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-(2-(N-benzyl-N-methyl-amino)-ethyl)-N-methylsulphonyl-amino)-aniline

$R_f$  value: 0.7 (silica gel, methylene chloride/methanol = 10:1)

$C_{34}H_{34}N_4O_5S$

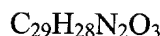
- 25 ESI mass spectrum:  $m/z = 609$   $[M-H]^-$

(52) 3-Z-[1-(4-cyclohexylamino-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-cyclohexyl-p-phenylenediamine

30

$R_f$  value: 0.8 (silica gel, methylene chloride/methanol = 10:1)

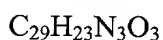


ESI mass spectrum:  $m/z = 451$   $[M-H]^-$

- 5 (53) 3-Z-[1-(4-(pyridin-4-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(pyridin-4-yl-methyl)-aniline

$R_f$  value: 0.6 (silica gel, methylene chloride/methanol/ammonia = 5:1:0.01)

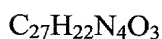


- 10 ESI mass spectrum:  $m/z = 460$   $[M-H]^-$

- (54) 3-Z-[1-(4-(imidazol-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

- 15 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(imidazol-1-yl-methyl)-aniline

$R_f$  value: 0.4 (silica gel, methylene chloride/methanol/ammonia = 10:1:0.01)



ESI mass spectrum:  $m/z = 449$   $[M-H]^-$

- 20 (55) 3-Z-[1-(4-(imidazol-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(imidazol-1-yl-methyl)-aniline

$R_f$  value: 0.4 (silica gel, methylene chloride/methanol/ammonia = 10:1:0.01)

- 25  $C_{27}H_{22}N_4O_3$

ESI mass spectrum:  $m/z = 449$   $[M-H]^-$

- (56) 3-Z-[1-(N-methyl-piperidine-4-yl-amino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

- 30 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-amino-1-methyl-piperidine

R<sub>f</sub> value: 0.3 (silica gel, methylene chloride/methanol = 5:1)

C<sub>23</sub>H<sub>25</sub>N<sub>3</sub>O<sub>3</sub>

ESI mass spectrum: m/z = 390 [M-H<sup>-</sup>]

- 5 (57) 3-Z-[1-(4-(imidazol-4-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(imidazol-4-yl-methyl)-aniline

R<sub>f</sub> value: 0.2 (silica gel, methylene chloride/methanol = 5:1)

- 10 C<sub>27</sub>H<sub>22</sub>N<sub>4</sub>O<sub>3</sub>

ESI mass spectrum: m/z = 449 [M-H<sup>-</sup>]

(58) 3-Z-[1-(4-((4-hydroxy-piperidin-1-yl)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

- 15 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((4-hydroxy-piperidin-1-yl)-methyl)-aniline

R<sub>f</sub> value: 0.1 (silica gel, methylene chloride/methanol = 10:1)

C<sub>29</sub>H<sub>29</sub>N<sub>3</sub>O<sub>3</sub>

ESI mass spectrum: m/z = 482 [M-H<sup>-</sup>]

20

(59) 3-Z-[1-(4-((4-methoxy-piperidin-1-yl)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((4-methoxy-piperidin-1-yl)-methyl)-aniline

- 25 R<sub>f</sub> value: 0.4 (silica gel, methylene chloride/methanol = 10:1)

C<sub>30</sub>H<sub>31</sub>N<sub>3</sub>O<sub>4</sub>

ESI mass spectrum: m/z = 496 [M-H<sup>-</sup>]

(60) 3-Z-[1-(4-benzyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

- 30 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-benzyl-aniline

R<sub>f</sub> value: 0.6 (silica gel, methylene chloride/methanol = 10:1)

C<sub>30</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub>

Melting point: 224°C

- 5 (61) 3-Z-[1-(4-(N-(3-trifluoroacetyl-amino-propyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(3-trifluoroacetyl-amino-propyl)-N-methylsulphonyl-p-phenylenediamine

R<sub>f</sub> value: 0.5 (aluminium oxide, methylene chloride/methanol = 20:1)

- 10 C<sub>29</sub>H<sub>27</sub>F<sub>3</sub>N<sub>4</sub>O<sub>6</sub>S

ESI mass spectrum: m/z = 615 [M-H<sup>-</sup>]

- (62) 3-Z-[1-(4-tert.butoxycarbonylmethyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

- 15 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and tert.butyl 4-aminophenylacetate

R<sub>f</sub> value: 0.5 (aluminium oxide, ethyl acetate)

C<sub>30</sub>H<sub>30</sub>N<sub>2</sub>O<sub>5</sub>

ESI mass spectrum: m/z = 497 [M-H<sup>-</sup>]

20

- (63) 3-Z-[1-(4-tert.butoxycarbonyl-anilino)-1-ethyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-ethylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-tert.butoxycarbonyl-aniline

- 25 R<sub>f</sub> value: 0.4 (aluminium oxide, methylene chloride/ethanol = 20:1)

C<sub>25</sub>H<sub>28</sub>N<sub>2</sub>O<sub>5</sub>

ESI mass spectrum: m/z = 435 [M-H<sup>-</sup>]

- 30 (64) 3-Z-[1-(4-(4-tert.butoxycarbonyl-piperazin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(4-tert.butoxycarbonyl-piperazin-1-yl-methyl)-aniline

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 10:1)

C<sub>33</sub>H<sub>36</sub>N<sub>4</sub>O<sub>5</sub>

5 ESI mass spectrum: m/z = 567 [M-H<sup>-</sup>]

(65) 3-Z-[1-(4-(1-methyl-imidazol-2-yl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(1-methyl-imidazol-2-yl)-aniline

R<sub>f</sub> value: 0.6 (silica gel, methylene chloride/methanol = 5:1)

C<sub>27</sub>H<sub>22</sub>N<sub>4</sub>O<sub>3</sub>

ESI mass spectrum: m/z = 449 [M-H<sup>-</sup>]

15 (66) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-3-nitro-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 6-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-3-amino-nitrobenzene

R<sub>f</sub> value: 0.6 (silica gel, methylene chloride/methanol = 5:1)

20 C<sub>28</sub>H<sub>29</sub>N<sub>5</sub>O<sub>7</sub>S

ESI mass spectrum: m/z = 578 [M-H<sup>-</sup>]

(67) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-3-amino-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

25 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-3-amino-aniline

R<sub>f</sub> value: 0.5 (aluminium oxide, methylene chloride/methanol = 20:1)

C<sub>28</sub>H<sub>31</sub>N<sub>5</sub>O<sub>5</sub>S

ESI mass spectrum: m/z = 548 [M-H<sup>-</sup>]

30

(68) 3-Z-[1-(4-((3-(N-benzyl-N-methyl-amino)-propyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-(3-(N-benzyl-N-methyl-amino)-propyl)-N-methylsulphonyl-amino)-aniline

5 R<sub>f</sub> value: 0.6 (silica gel, methylene chloride/methanol = 10:1)

C<sub>35</sub>H<sub>36</sub>N<sub>4</sub>O<sub>5</sub>S

ESI mass spectrum: m/z = 623 [M-H<sup>-</sup>]

(69) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-3-chloro-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

10 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-3-chloro-aniline

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 10:1)

C<sub>28</sub>H<sub>29</sub>ClN<sub>4</sub>O<sub>5</sub>S

15 ESI mass spectrum: m/z = 567/569 [M-H<sup>-</sup>]

(70) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-dimethylaminomethylcarbonyl-N-methyl-p-phenylenediamine

20 R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

C<sub>28</sub>H<sub>28</sub>N<sub>4</sub>O<sub>4</sub>

ESI mass spectrum: m/z = 483 [M-H<sup>-</sup>]

(71) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-aniline

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

30 C<sub>29</sub>H<sub>30</sub>N<sub>4</sub>O<sub>4</sub>

ESI mass spectrum: m/z = 497 [M-H<sup>-</sup>]

(72) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-propionyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone  
and 4-(N-(2-dimethylamino-ethyl)-N-propionyl-amino)-aniline

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>4</sub>

ESI mass spectrum: m/z = 511 [M-H]

(73) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-butyryl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone  
and 4-(N-(2-dimethylamino-ethyl)-N-butyryl-amino)-aniline

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

C<sub>31</sub>H<sub>34</sub>N<sub>4</sub>O<sub>4</sub>

ESI mass spectrum: m/z = 525 [M-H]

(74) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-isobutyryl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone  
and 4-(N-(2-dimethylamino-ethyl)-N-isobutyryl-amino)-aniline

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

C<sub>31</sub>H<sub>34</sub>N<sub>4</sub>O<sub>4</sub>

ESI mass spectrum: m/z = 525 [M-H]

(75) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-benzoyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone  
and 4-(N-(2-dimethylamino-ethyl)-N-benzoyl-amino)-aniline

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

C<sub>34</sub>H<sub>32</sub>N<sub>4</sub>O<sub>4</sub>

ESI mass spectrum:  $m/z = 559$   $[M-H]^-$

(76) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-3-amino-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

5 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-3-amino-aniline

$R_f$  value: 0.5 (aluminium oxide, methylene chloride/methanol = 20:1)

$C_{29}H_{31}N_5O_4$

ESI mass spectrum:  $m/z = 512$   $[M-H]^-$

10

(77) 3-Z-[1-(4-(4-hydroxymethyl-piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(4-hydroxymethyl-piperidin-1-yl-methyl-amino)-aniline

15  $R_f$  value: 0.3 (silica gel, methylene chloride/methanol = 5:1)

$C_{30}H_{31}N_3O_4$

ESI mass spectrum:  $m/z = 496$   $[M-H]^-$

(78) 3-Z-[1-(4-(2-(4-hydroxy-piperidin-1-yl)-ethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

20

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(2-(4-hydroxy-piperidin-1-yl)-ethyl-amino)-aniline

$R_f$  value: 0.3 (silica gel, methylene chloride/methanol = 5:1)

$C_{30}H_{31}N_3O_4$

25 ESI mass spectrum:  $m/z = 496$   $[M-H]^-$

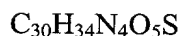
(79) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-propylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(2-dimethylamino-ethyl)-N-propylsulphonyl-p-phenylenediamine

30

$R_f$  value: 0.5 (silica gel, methylene chloride/methanol = 9:1)



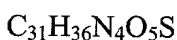


ESI mass spectrum:  $m/z = 561$   $[M-H^-]$

- 5 (80) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-butylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(2-dimethylamino-ethyl)-N-butylsulphonyl-p-phenylenediamine

$R_f$  value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

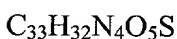


- 10 ESI mass spectrum:  $m/z = 575$   $[M-H^-]$

- (81) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-phenylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

- 15 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(2-dimethylamino-ethyl)-N-phenylsulphonyl-p-phenylenediamine

$R_f$  value: 0.5 (silica gel, methylene chloride/methanol = 9:1)



ESI mass spectrum:  $m/z = 595$   $[M-H^-]$

- 20 (82) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-benzylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(2-dimethylamino-ethyl)-N-benzylsulphonyl-p-phenylenediamine

$R_f$  value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

- 25  $C_{34}H_{34}N_4O_5S$

ESI mass spectrum:  $m/z = 609$   $[M-H^-]$

- (83) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-ethylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

- 30 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(2-dimethylamino-ethyl)-N-ethylsulphonyl-p-phenylenediamine

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

C<sub>29</sub>H<sub>32</sub>N<sub>4</sub>O<sub>5</sub>S

ESI mass spectrum: m/z = 547 [M-H<sup>-</sup>]

- 5 (84) 3-Z-[1-(4-((imidazolidin-2,4-dion-5-yl)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((imidazolidin-2,4-dion-5-yl)-methyl)-aniline

R<sub>f</sub> value: 0.6 (silica gel, methylene chloride/methanol = 5:1)

- 10 C<sub>27</sub>H<sub>22</sub>N<sub>4</sub>O<sub>5</sub>

ESI mass spectrum: m/z = 481 [M-H<sup>-</sup>]

- (85) 3-Z-[1-(4-((3-hydroxy-pyrrolidin-1-yl)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

- 15 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((3-hydroxy-pyrrolidin-1-yl)-methyl)-aniline

R<sub>f</sub> value: 0.1 (silica gel, methylene chloride/methanol = 10:1)

C<sub>28</sub>H<sub>27</sub>N<sub>3</sub>O<sub>4</sub>

ESI mass spectrum: m/z = 468 [M-H<sup>-</sup>]

20

- (86) 3-Z-[1-(4-(cyclohexyl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(cyclohexyl-methyl)-aniline (Eur. J. Med. Chem. Chim. Ther. 1992, 27, 537-544)

- 25 R<sub>f</sub> value: 0.6 (silica gel, methylene chloride/methanol = 10:1)

C<sub>30</sub>H<sub>30</sub>N<sub>2</sub>O<sub>3</sub>

ESI mass spectrum: m/z = 465 [M-H<sup>-</sup>]

- (87) 3-Z-[1-(4-(cyclohexyl-carbonyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone
- 30

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(cyclohexyl-carbonyl)-aniline

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 10:1)

C<sub>30</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>

5 ESI mass spectrum: m/z = 479 [M-H<sup>-</sup>]

(88) 3-Z-[1-(4-diethylaminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(diethylamino-methyl)-aniline

R<sub>f</sub> value: 0.4 (silica gel, methylene chloride/methanol = 10:1)

C<sub>28</sub>H<sub>29</sub>N<sub>3</sub>O<sub>3</sub>

ESI mass spectrum: m/z = 454 [M-H<sup>-</sup>]

15 (89) 3-Z-[1-(4-(N-(n-hexyl)-N-methyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-(n-hexyl)-N-methyl-aminomethyl)-aniline

R<sub>f</sub> value: 0.6 (silica gel, methylene chloride/methanol = 10:1)

20 C<sub>31</sub>H<sub>35</sub>N<sub>3</sub>O<sub>3</sub>

ESI mass spectrum: m/z = 496 [M-H<sup>-</sup>]

(90) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-(furan-2-carbonyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

25 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-(2-dimethylamino-ethyl)-N-(furan-2-carbonyl)-amino)-aniline

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

C<sub>32</sub>H<sub>30</sub>N<sub>4</sub>O<sub>5</sub>

ESI mass spectrum: m/z = 549 [M-H<sup>-</sup>]

30

(91) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-(2-methoxy-benzoyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-(2-dimethylamino-ethyl)-N-(2-methoxy-benzoyl)-amino)-aniline

5 R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

C<sub>35</sub>H<sub>34</sub>N<sub>4</sub>O<sub>5</sub>

ESI mass spectrum: m/z = 589 [M-H<sup>-</sup>]

(92) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-(pyridine-3-carbonyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

10 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-(2-dimethylamino-ethyl)-N-(pyridine-3-carbonyl)-amino)-aniline

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

C<sub>33</sub>H<sub>31</sub>N<sub>5</sub>O<sub>4</sub>

15 ESI mass spectrum: m/z = 560 [M-H<sup>-</sup>]

(93) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-(phenyl-acetyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

20 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-(2-dimethylamino-ethyl)-N-(phenyl-acetyl)-amino)-aniline

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

C<sub>35</sub>H<sub>34</sub>N<sub>4</sub>O<sub>4</sub>

ESI mass spectrum: m/z = 573 [M-H<sup>-</sup>]

25 (94) 3-Z-[1-(4-(N-ethyl-N-methyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-ethyl-N-methyl-aminomethyl)-aniline

R<sub>f</sub> value: 0.3 (silica gel, methylene chloride/methanol = 10:1)

30 C<sub>27</sub>H<sub>27</sub>N<sub>3</sub>O<sub>3</sub>

ESI mass spectrum: m/z = 440 [M-H<sup>-</sup>]

(95) 3-Z-[1-(4-(imidazol-2-yl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone  
5 and 4-(imidazol-2-yl)-aniline

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 10:1)

C<sub>26</sub>H<sub>20</sub>N<sub>4</sub>O<sub>3</sub>

ESI mass spectrum: m/z = 435 [M-H<sup>-</sup>]

10 (96) 3-Z-[1-(4-(1-ethyl-imidazol-2-yl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone  
and 4-(1-ethyl-imidazol-2-yl)-aniline

R<sub>f</sub> value: 0.4 (silica gel, methylene chloride/methanol = 10:1)

15 C<sub>28</sub>H<sub>24</sub>N<sub>4</sub>O<sub>3</sub>

ESI mass spectrum: m/z = 463 [M-H<sup>-</sup>]

(97) 3-Z-[1-(4-(1-benzyl-imidazol-2-yl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

20 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone  
and 4-(1-benzyl-imidazol-2-yl)-aniline

R<sub>f</sub> value: 0.3 (silica gel, methylene chloride/methanol = 20:1)

C<sub>33</sub>H<sub>26</sub>N<sub>4</sub>O<sub>3</sub>

ESI mass spectrum: m/z = 525 [M-H<sup>-</sup>]

25

(98) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-isopropylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone  
and N-(2-dimethylamino-ethyl)-N-isopropylsulphonyl-p-phenylenediamine

30 R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

C<sub>30</sub>H<sub>34</sub>N<sub>4</sub>O<sub>5</sub>S

ESI mass spectrum:  $m/z = 561$   $[M-H^-]$

(99) 3-Z-[1-(4-(N-(piperidin-1-yl-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

5 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(piperidin-1-yl-methylcarbonyl)-N-methyl-p-phenylenediamine

$R_f$  value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

$C_{31}H_{32}N_4O_4$

ESI mass spectrum:  $m/z = 523$   $[M-H^-]$

10

(100) 3-Z-[1-(4-(N-(morpholin-4-yl-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(morpholin-4-yl-methylcarbonyl)-N-methyl-p-phenylenediamine

15  $R_f$  value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

$C_{30}H_{30}N_4O_5$

ESI mass spectrum:  $m/z = 525$   $[M-H^-]$

(101) 3-Z-[1-(4-(N-((4-benzyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

20 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-((4-benzyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-p-phenylenediamine

$R_f$  value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

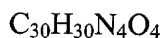
$C_{37}H_{37}N_5O_4$

25 ESI mass spectrum:  $m/z = 614$   $[M-H^-]$

(102) 3-Z-[1-(4-(N-(pyrrolidin-1-yl-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

30 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(pyrrolidin-1-yl-methylcarbonyl)-N-methyl-p-phenylenediamine

$R_f$  value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

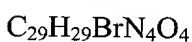


ESI mass spectrum:  $m/z = 509 [M-H^-]$

- 5 (103) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-3-bromo-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-3-bromo-aniline

$R_f$  value: 0.6 (silica gel, methylene chloride/methanol = 5:1)

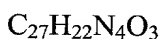


- 10 ESI mass spectrum:  $m/z = 575/577 [M-H^-]$

- (104) 3-Z-[1-(4-(5-methyl-imidazol-4-yl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

- 15 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(5-methyl-imidazol-4-yl)-aniline

$R_f$  value: 0.5 (silica gel, methylene chloride/methanol/ammonia = 10:1:0.01)



ESI mass spectrum:  $m/z = 449 [M-H^-]$

- 20 (105) 3-Z-[1-(4-(N-((2-dimethylamino-ethyl)-carbonyl)-N-isopropyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-((2-dimethylamino-ethyl)-carbonyl)-N-isopropyl-p-phenylenediamine

$R_f$  value: 0.1 (silica gel, methylene chloride/methanol = 10:1)

- 25  $C_{31}H_{34}N_4O_4$

ESI mass spectrum:  $m/z = 525 [M-H^-]$

- (106) 3-Z-[1-(4-(N-((2-dimethylamino-ethyl)-carbonyl)-N-benzyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

- 30 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-((2-dimethylamino-ethyl)-carbonyl)-N-benzyl-p-phenylenediamine

R<sub>f</sub> value: 0.1 (silica gel, methylene chloride/methanol = 10:1)

C<sub>31</sub>H<sub>34</sub>N<sub>4</sub>O<sub>4</sub>

ESI mass spectrum: m/z = 525 [M-H<sup>-</sup>]

- 5 (107) 3-Z-[1-(4-(N-butyl-N-tert.butoxycarbonyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-butyl-N-tert.butoxycarbonyl-aminomethyl)-aniline

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

- 10 C<sub>33</sub>H<sub>37</sub>N<sub>3</sub>O<sub>5</sub>

ESI mass spectrum: m/z = 554 [M-H<sup>-</sup>]

(108) 3-Z-[1-(4-(N-((N-aminocarbonylmethyl-N-methyl-amino)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

- 15 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(N-aminocarbonylmethyl-N-methyl-amino)-methylcarbonyl)-N-methyl-p-phenylenediamine

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

C<sub>29</sub>H<sub>29</sub>N<sub>5</sub>O<sub>5</sub>

- 20 ESI mass spectrum: m/z = 526 [M-H<sup>-</sup>]

(109) 3-Z-[1-(4-(N-((N-benzyl-N-methyl-amino)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

- 25 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-((N-benzyl-N-methyl-amino)-methylcarbonyl)-N-methyl-p-phenylenediamine

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

C<sub>34</sub>H<sub>32</sub>N<sub>4</sub>O<sub>4</sub>

ESI mass spectrum: m/z = 559 [M-H<sup>-</sup>]

- 30 (110) 3-Z-[1-(4-(N-(di-(2-methoxyethyl)-amino-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone



Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(di-(2-methoxyethyl)-amino-methylcarbonyl)-N-methyl-p-phenylenediamine

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

C<sub>32</sub>H<sub>36</sub>N<sub>4</sub>O<sub>6</sub>

5 ESI mass spectrum: m/z = 571 [M-H<sup>-</sup>]

(111) 3-Z-[1-(4-(N-((2-(4-tert.butoxycarbonyl-piperazin-1-yl)-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone

10 and N-((2-(4-tert.butoxycarbonyl-piperazin-1-yl)-ethyl)-carbonyl)-N-methyl-p-phenylenediamine

R<sub>f</sub> value: 0.8 (silica gel, methylene chloride/methanol = 5:1)

C<sub>36</sub>H<sub>41</sub>N<sub>5</sub>O<sub>6</sub>

ESI mass spectrum: m/z = 638 [M-H<sup>-</sup>]

15

(112) 3-Z-[1-(4-(N-((2-(piperidin-1-yl)-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone

and N-((2-(piperidin-1-yl)-ethyl)-carbonyl)-N-methyl-p-phenylenediamine

20 R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 5:1)

C<sub>32</sub>H<sub>34</sub>N<sub>4</sub>O<sub>4</sub>

ESI mass spectrum: m/z = 537 [M-H<sup>-</sup>]

(113) 3-Z-[1-(4-(N-((2-(N-benzyl-N-methyl-amino)-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

25

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone

and N-((2-(N-benzyl-N-methyl-amino)-ethyl)-carbonyl)-N-methyl-p-phenylenediamine

R<sub>f</sub> value: 0.4 (silica gel, methylene chloride/methanol = 10:1)

C<sub>35</sub>H<sub>34</sub>N<sub>4</sub>O<sub>4</sub>

30 ESI mass spectrum: m/z = 573 [M-H<sup>-</sup>]

(114) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-isopropyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(dimethylaminomethylcarbonyl)-N-isopropyl-p-phenylenediamine

5  $R_f$  value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

$C_{30}H_{32}N_4O_4$

ESI mass spectrum:  $m/z = 511 [M-H^-]$

10 (115) 3-Z-[1-(4-(N-(piperidin-1-yl-methylcarbonyl)-N-isopropyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(piperidin-1-yl-methylcarbonyl)-N-isopropyl-p-phenylenediamine

$R_f$  value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

$C_{33}H_{36}N_4O_4$

15 ESI mass spectrum:  $m/z = 551 [M-H^-]$

(116) 3-Z-[1-(4-(N-((4-tert.butoxycarbonyl-piperazin-1-yl)-methylcarbonyl)-N-isopropyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

20 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-((4-tert.butoxycarbonyl-piperazin-1-yl)-methylcarbonyl)-N-isopropyl-p-phenylenediamine

$R_f$  value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

$C_{37}H_{43}N_5O_6$

ESI mass spectrum:  $m/z = 652 [M-H^-]$

25

(117) 3-Z-[1-(4-(N-((N-benzyl-N-methyl-amino)-methylcarbonyl)-N-benzyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-((N-benzyl-N-methyl-amino)-methylcarbonyl)-N-benzyl-p-phenylenediamine

30  $R_f$  value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

$C_{40}H_{36}N_4O_4$

ESI mass spectrum:  $m/z = 635$   $[M-H]^-$

(118) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-benzyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

- 5 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(dimethylaminomethyl-carbonyl)-N-benzyl-p-phenylenediamine

$R_f$  value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

$C_{34}H_{32}N_4O_4$

ESI mass spectrum:  $m/z = 559$   $[M-H]^-$

10

(119) 3-Z-[1-(4-(N-(piperidin-1-yl-methylcarbonyl)-N-benzyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(5-methyl-imidazol-4-yl)-aniline

- 15  $R_f$  value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

$C_{37}H_{36}N_4O_4$

ESI mass spectrum:  $m/z = 559$   $[M-H]^-$

(120) 3-Z-[1-(4-(1,2,4-triazol-2-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

20

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(1,2,4-triazol-1-yl-methyl)-aniline

$R_f$  value: 0.5 (silica gel, methylene chloride/methanol = 10:1)

$C_{26}H_{21}N_5O_3$

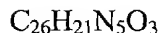
- 25 ESI mass spectrum:  $m/z = 450$   $[M-H]^-$

(121) 3-Z-[1-(4-(1,2,3-triazol-2-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(1,2,3-triazol-2-yl-methyl)-aniline

30

$R_f$  value: 0.5 (silica gel, methylene chloride/methanol = 20:1)

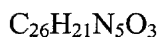


ESI mass spectrum:  $m/z = 450$   $[M-H^-]$

(122) 3-Z-[1-(4-(1,2,3-triazol-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(1,2,3-triazol-1-yl-methyl)-aniline

$R_f$  value: 0.4 (silica gel, methylene chloride/methanol = 9:1)

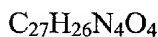


ESI mass spectrum:  $m/z = 450$   $[M-H^-]$

(123) 3-Z-[1-(4-((N-aminocarbonylmethyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((N-aminocarbonylmethyl-N-methyl-amino)-methyl)-aniline

$R_f$  value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

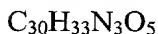


ESI mass spectrum:  $m/z = 469$   $[M-H^-]$

(124) 3-Z-[1-(4-((di-(2-methoxy-ethyl)-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((di-(2-methoxy-ethyl)-amino)-methyl)-aniline

$R_f$  value: 0.5 (silica gel, methylene chloride/methanol = 9:1)



ESI mass spectrum:  $m/z = 514$   $[M-H^-]$

(125) 3-Z-[1-(4-(pyrrolidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(pyrrolidin-1-yl-methyl)-aniline

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

C<sub>28</sub>H<sub>27</sub>N<sub>3</sub>O<sub>3</sub>

ESI mass spectrum: m/z = 452 [M-H]

- 5 (126) 3-Z-[1-(4-((di-(2-hydroxy-ethyl)-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((di-(2-hydroxy-ethyl)-amino)-methyl)-aniline

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

- 10 C<sub>28</sub>H<sub>29</sub>N<sub>3</sub>O<sub>5</sub>

ESI mass spectrum: m/z = 486 [M-H]

(127) 3-Z-[1-(4-((N-ethoxycarbonylmethyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

- 15 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((N-ethoxycarbonylmethyl-N-methyl-amino)-methyl)-aniline

R<sub>f</sub> value: 0.5 (aluminium oxide, methylene chloride/ethanol = 40:1)

C<sub>29</sub>H<sub>29</sub>N<sub>3</sub>O<sub>5</sub>

ESI mass spectrum: m/z = 498 [M-H]

20

(128) 3-Z-[1-(4-(azetidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(azetidin-1-yl-methyl)-aniline

- 25 R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol/ammonia = 9:1:0.5)

C<sub>27</sub>H<sub>25</sub>N<sub>3</sub>O<sub>3</sub>

ESI mass spectrum: m/z = 438 [M-H]

- 30 (129) 3-Z-[1-(4-(N-propyl-N-tert.butoxycarbonyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-propyl-N-tert.butoxycarbonyl-aminomethyl)-aniline

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

C<sub>32</sub>H<sub>35</sub>N<sub>3</sub>O<sub>5</sub>

5 ESI mass spectrum: m/z = 540 [M-H<sup>-</sup>]

(130) 3-Z-[1-(4((N-(2-(2-methoxy-ethoxy)-ethyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone

10 and 4-((N-(2-(2-methoxy-ethoxy)-ethyl)-N-methyl-amino)-methyl)-aniline

R<sub>f</sub> value: 0.4 (silica gel, methylene chloride/methanol = 9:1)

C<sub>30</sub>H<sub>33</sub>N<sub>3</sub>O<sub>5</sub>

ESI mass spectrum: m/z = 514 [M-H<sup>-</sup>]

15 (131) 3-Z-[1-(4-((N-(tert.butoxycarbonyl-3-amino-propyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone

and 4-(N-(N-tert.butoxycarbonyl-3-amino-propyl)-N-methyl-aminomethyl)-aniline

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

20 C<sub>33</sub>H<sub>38</sub>N<sub>4</sub>O<sub>5</sub>

ESI mass spectrum: m/z = 571 [M+H<sup>+</sup>]

(132) 3-Z-[1-(4-((N-(methylcarbamoyl-methyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

25 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone

and 4-((N-(methylcarbamoyl-methyl)-N-methyl-amino)-methyl)-aniline

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

C<sub>28</sub>H<sub>28</sub>N<sub>4</sub>O<sub>4</sub>

ESI mass spectrum: m/z = 483 [M-H<sup>-</sup>]

30

(133) 3-Z-[1-(4-((N-(dimethylcarbamoyl-methyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((N-(dimethylcarbamoyl-methyl)-N-methyl-amino)-methyl)-aniline

5 R<sub>f</sub> value: 0.3 (silica gel, methylene chloride/methanol = 10:1)

C<sub>29</sub>H<sub>30</sub>N<sub>4</sub>O<sub>4</sub>

ESI mass spectrum: m/z = 497 [M-H<sup>-</sup>]

(134) 3-Z-[1-(4-methyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

10 Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-methyl-aniline

R<sub>f</sub> value: 0.4 (silica gel, methylene chloride/methanol = 9:1)

C<sub>24</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>

ESI mass spectrum: m/z = 383 [M-H<sup>-</sup>]

15 (135) 3-Z-[1-(4-((N-propyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((N-propyl-N-methyl-amino)-methyl)-aniline

20 R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

C<sub>28</sub>H<sub>29</sub>N<sub>3</sub>O<sub>3</sub>

ESI mass spectrum: m/z = 454 [M-H<sup>-</sup>]

(136) 3-Z-[1-(4-((N-(2-hydroxy-ethyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

25

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((N-(2-hydroxy-ethyl)-N-methyl-amino)-methyl)-aniline

R<sub>f</sub> value: 0.5 (aluminium oxide, methylene chloride/ethanol = 40:1)

C<sub>27</sub>H<sub>27</sub>N<sub>3</sub>O<sub>4</sub>

30 ESI mass spectrum: m/z = 456 [M-H<sup>-</sup>]

(137) 3-Z-[1-(4-((N-(2-dimethylamino-ethyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((N-(2-dimethylamino-ethyl)-N-methyl-amino)-methyl)-aniline

5  $R_f$  value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

$C_{29}H_{32}N_4O_3$

ESI mass spectrum:  $m/z = 483$   $[M-H^-]$

10 (138) 3-Z-[1-(4-((N-(3-dimethylamino-propyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((N-(3-dimethylamino-propyl)-N-methyl-amino)-methyl)-aniline aniline

$R_f$  value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

15  $C_{30}H_{34}N_4O_3$

ESI mass spectrum:  $m/z = 497$   $[M-H^-]$

(139) 3-Z-[1-(4-(3-oxo-piperazin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

20

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(3-oxo-piperazin-1-yl-methyl)-aniline aniline

$R_f$  value: 0.46 (silica gel, methylene chloride/methanol = 9:1)

$C_{28}H_{26}N_4O_4$

25 ESI mass spectrum:  $m/z = 481$   $[M-H^-]$

#### Example 4

30 3-Z-[1-(4-carboxy-anilino)-1-phenyl-methylene]-6-ethoxy-carbonyl-2-indolinone

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485 mg of 3-Z-[1-(4-tert.butoxycarbonyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone are dissolved in 15 ml of methylene chloride and 6.0 ml of trifluoroacetic acid are added. The mixture is stirred for 2 hours at room temperature. Then the solvent is removed and the residue recrystallised from ether.

5 Yield: 375 mg (87 % of theory),

R<sub>f</sub> value: 0.3 (silica gel, methylene chloride/methanol = 10:1)

C<sub>25</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>

Mass spectrum: m/z = 428 [M<sup>+</sup>]

10 The following compounds are prepared analogously to Example 4:

(1) 3-Z-[1-(4-aminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(N-tert.butoxycarbonyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

15 R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol/ammonia = 5:1:0.01)

C<sub>24</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>

ESI mass spectrum: m/z = 398 [M-H<sup>-</sup>]

(2) 3-Z-[1-(4-ethylaminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-

20 indolinone

Prepared from 3-Z-[1-(4-(N-tert.butoxycarbonyl-ethylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

R<sub>f</sub> value: 0.4 (silica gel, methylene chloride/methanol/ammonia = 10:1:0.01)

25 C<sub>26</sub>H<sub>25</sub>N<sub>3</sub>O<sub>3</sub>

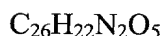
ESI mass spectrum: m/z = 426 [M-H<sup>-</sup>]

(3) 3-Z-[1-(4-carboxymethyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-tert.butoxycarbonylmethyl-anilino)-1-phenyl-methylene]-6-

30 ethoxycarbonyl-2-indolinone

R<sub>f</sub> value: 0.1 (aluminium oxide, methylene chloride/ethanol/ammonia = 5:1:0.01)

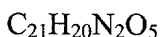


ESI mass spectrum:  $m/z = 441$   $[M-H]^-$

(4) 3-Z-[1-(4-carboxy-anilino)-1-ethyl-methylene]-6-ethoxycarbonyl-2-indolinone

5 Prepared from 3-Z-[1-(4-tert.butoxycarbonyl-anilino)-1-ethyl-methylene]-6-ethoxycarbonyl-2-indolinone

$R_f$  value: 0.1 (aluminium oxide, methylene chloride/ethanol = 20:1)



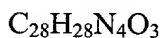
ESI mass spectrum:  $m/z = 379$   $[M-H]^-$

10

(5) 3-Z-[1-(4-(piperazin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(4-tert.butoxycarbonyl-piperazin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

15  $R_f$  value: 0.1 (silica gel, methylene chloride/methanol/ammonia = 10:1:0.01)



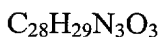
ESI mass spectrum:  $m/z = 469$   $[M+H]^+$

(6) 3-Z-[1-(4-butylaminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

20

Prepared from 3-Z-[1-(4-(N-butyl-N-tert.butoxycarbonyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

$R_f$  value: 0.5 (silica gel, methylene chloride/methanol = 9:1)



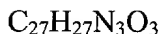
25 ESI mass spectrum:  $m/z = 454$   $[M-H]^-$

(7) 3-Z-[1-(4-ethylaminomethyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(N-tert.butoxycarbonyl-N-ethyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

30

$R_f$  value: 0.3 (silica gel, methylene chloride/methanol/ammonia = 10:1:0.01)

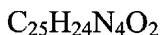


ESI mass spectrum:  $m/z = 442 [M+H^+]$

(8) 3-Z-[1-(4-ethylaminomethyl-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

5 Prepared from 3-Z-[1-(4-(N-tert.butoxycarbonyl-ethylaminomethyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

$R_f$  value: 0.2 (silica gel, methylene chloride/methanol/ammonia = 5:1:0.01)



ESI mass spectrum:  $m/z = 411 [M-H^-]$

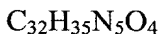
10

(9) 3-Z-[1-(4-(N-(piperazin-1-yl-methylcarbonyl)-N-isopropyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(N-((4-tert.butoxycarbonyl-piperazin-1-yl)-methylcarbonyl)-N-isopropyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

15

$R_f$  value: 0.35 (silica gel, methylene chloride/methanol = 9:1)



ESI mass spectrum:  $m/z = 552 [M-H^-]$

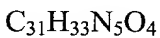
20

(10) 3-Z-[1-(4-(N-((2-(piperazin-1-yl)-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(N-((2-(4-tert.butoxycarbonyl-piperazin-1-yl)-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

25

$R_f$  value: 0.4 (silica gel, methylene chloride/methanol/ammonia = 5:1:0.01)



ESI mass spectrum:  $m/z = 540 [M+H^+]$

(11) 3-Z-[1-(4-(N-propyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-

30

methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(N-propyl-N-tert.butoxycarbonyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

R<sub>f</sub> value: 0.35 (silica gel, methylene chloride/methanol = 9:1)

C<sub>27</sub>H<sub>27</sub>N<sub>3</sub>O<sub>3</sub>

5 ESI mass spectrum: m/z = 440 [M-H<sup>-</sup>]

(12) 3-Z-[1-(4-((N-(3-amino-propyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-((N-(tert.butoxycarbonyl-3-amino-propyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

10

R<sub>f</sub> value: 0.35 (silica gel, methylene chloride/methanol = 9:1)

C<sub>28</sub>H<sub>30</sub>N<sub>4</sub>O<sub>3</sub>

ESI mass spectrum: m/z = 471 [M+H<sup>+</sup>]

15 Example 5

3-Z-[1-(4-methylaminomethyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

---

20 100 mg of 3-Z-[1-(4-(N-benzyl-N-methyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone are dissolved in 20 ml of ethanol, 0.2 ml of 1N hydrochloric acid are added and the mixture is hydrogenated for 70 minutes at room temperature and 50 psi hydrogen pressure. The reaction solution is filtered and the filtrate concentrated by rotary evaporation. The residue is dried *in vacuo* at 100°C.

25 Yield: 50 mg (53 % of theory),

R<sub>f</sub> value: 0.3 (silica gel, methylene chloride/ethanol/ammonia = 5:1:0.01)

C<sub>26</sub>H<sub>25</sub>N<sub>3</sub>O<sub>3</sub>

ESI mass spectrum: m/z = 426 [M-H<sup>-</sup>]

30 The following compounds are prepared analogously to Example 5:

(1) 3-Z-[1-(4-methylaminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(N-benzyl-N-methyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

5  $R_f$  value: 0.2 (silica gel, methylene chloride/methanol/ammonia = 10:1:0.01)

$C_{25}H_{23}N_3O_3$

ESI mass spectrum:  $m/z = 412$   $[M-H^-]$

(2) 3-Z-[1-(4-(N-(2-methylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

10 Prepared from 3-Z-[1-(4-((2-(N-benzyl-N-methyl-amino)-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

$R_f$  value: 0.3 (silica gel, methylene chloride/methanol/ammonia = 10:1:0.01)

$C_{27}H_{28}N_4O_5S$

15 ESI mass spectrum:  $m/z = 519$   $[M-H^-]$

(3) 3-Z-[1-(4-(N-(2-amino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(N-cyanomethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

20

$R_f$  value: 0.5 (silica gel, methylene chloride/methanol/ammonia = 5:1:0.01)

$C_{26}H_{26}N_4O_5S$

ESI mass spectrum:  $m/z = 505$   $[M-H^-]$

(4) 3-Z-[1-(4-(N-(3-methylamino-propyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(N-(3-(N-benzyl-N-methyl-amino)-propyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

$R_f$  value: 0.3 (silica gel, methylene chloride/methanol/ammonia = 5:1:0.01)

30  $C_{28}H_{30}N_4O_5S$

ESI mass spectrum:  $m/z = 533$   $[M-H^-]$

(5) 3-Z-[1-(4-(N-(piperazin-1-yl-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(N-((4-benzyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 9:1)

C<sub>30</sub>H<sub>31</sub>N<sub>5</sub>O<sub>4</sub>

ESI mass spectrum: m/z = 524 [M-H]<sup>+</sup>

10 (6) 3-Z-[1-(4-(N-(methylamino-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(N-((N-benzyl-N-methyl-amino)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

R<sub>f</sub> value: 0.3 (silica gel, methylene chloride/methanol = 9:1)

15 C<sub>27</sub>H<sub>26</sub>N<sub>4</sub>O<sub>4</sub>

ESI mass spectrum: m/z = 469 [M-H]<sup>+</sup>

(7) 3-Z-[1-(4-(N-((2-methylamino-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

20 Prepared from 3-Z-[1-(4-(N-((N-benzyl-N-methyl-amino)-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

R<sub>f</sub> value: 0.3 (silica gel, methylene chloride/methanol/ammonia = 5:1:0.01)

C<sub>28</sub>H<sub>28</sub>N<sub>4</sub>O<sub>4</sub>

ESI mass spectrum: m/z = 483 [M-H]<sup>+</sup>

25

### Example 6

3-Z-[1-(4-ureidomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

---

30 300 mg of 3-Z-[1-(4-aminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone are dissolved in 15 ml of methanol and 200 ml of triethylamine are added. Then

400 mg of potassium cyanate in 5 ml of water are added. After 2 days of stirring at room temperature the reaction solution is concentrated by rotary evaporation, the residue taken up in methylene chloride and washed once with water and once with saturated sodium chloride solution. The organic phase is dried over sodium sulphate and concentrated by rotary evaporation. The residue is dried *in vacuo* at 100°C.

Yield: 100 mg of (21 % of theory),

R<sub>f</sub> value: 0.7 (silica gel, methylene chloride/methanol = 5:1)

C<sub>25</sub>H<sub>22</sub>N<sub>4</sub>O<sub>4</sub>

ESI mass spectrum: m/z = 441 [M-H]<sup>-</sup>

### Example 7

3-Z-[1-(4-guanidinomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

---

300 mg of 3-Z-[1-(4-aminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone are dissolved in 5 ml of dimethylformamide and 300 ml of triethylamine are added. Then 700 mg of 3,5-dimethylpyrazol-1-carboxylic acid amidine in 5 ml of dimethylformamide are added. After one day of stirring at room temperature the reaction solution is concentrated by rotary evaporation. The residue is dried at 100°C *in vacuo*.

Yield: 200 mg (87 % of theory),

R<sub>f</sub> value: 0.1 (Reversed phase RP 8, methanol/five percent saline solution = 6:4)

C<sub>25</sub>H<sub>23</sub>N<sub>5</sub>O<sub>3</sub>

Mass spectrum: m/z = 441 [M]<sup>+</sup>

### Example 8

3-Z-[1-(4-acetylaminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

---

100 mg of 3-Z-[1-(4-aminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone are dissolved in 5 ml of glacial acetic acid, 0.1 ml of acetic anhydride is added and the mixture is stirred for 10 minutes at room temperature. After this time the reaction solution is poured onto saturated soda solution and extracted four times with methylene chloride. The combined organic phases are washed with saturated saline solution, dried over sodium sulphate and concentrated by rotary evaporation. The residue is dried at 100°C *in vacuo*.

Yield: 20 mg (23 % of theory),

R<sub>f</sub> value: 0.4 (silica gel, methylene chloride/methanol = 10:1)

C<sub>26</sub>H<sub>23</sub>N<sub>3</sub>O<sub>4</sub>

ESI mass spectrum: m/z = 440 [M-H]<sup>-</sup>

The following compounds are prepared analogously to Example 8:

(1) 3-Z-[1-(4-(N-methylsulphonyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-aminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone and methanesulphonyl chloride/triethylamine

R<sub>f</sub> value: 0.7 (silica gel, methylene chloride/methanol = 5:1)

C<sub>25</sub>H<sub>23</sub>N<sub>3</sub>O<sub>5</sub>S

ESI mass spectrum: m/z = 476 [M-H]<sup>-</sup>

(2) 3-Z-[1-(4-(4-benzoyl-piperazin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(piperazin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone and benzoyl chloride

R<sub>f</sub> value: 0.7 (silica gel, methylene chloride/methanol = 10:1)

C<sub>35</sub>H<sub>32</sub>N<sub>4</sub>O<sub>4</sub>

ESI mass spectrum: m/z = 571 [M-H]<sup>-</sup>



(3) 3-Z-[1-(4-((N-(3-acetylamino-propyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-((N-(3-amino-propyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

5  $R_f$  value: 0.3 (silica gel, methylene chloride/methanol = 9:1)

$C_{30}H_{32}N_4O_4$

ESI mass spectrum:  $m/z = 511 [M-H^-]$

### Example 9

10

3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone

---

0.8 g of 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone are dissolved in 30 ml of ethanol, 8.3 ml of 1N sodium

15 hydroxide solution are added and the mixture is stirred for 1 hour at 80°C. After cooling, it is neutralised with 8.3 ml of 1N hydrochloric acid. The precipitate formed is suction filtered, washed with water, ethanol and ether and dried *in vacuo* at 100°C.

Yield: 0.7 g of (89 % of theory),

$R_f$  value: 0.2 (silica gel, methylene chloride/methanol = 5:2)

20  $C_{28}H_{27}N_3O_3$

Mass spectrum:  $m/z = 453 [M^+]$

The following compounds are prepared analogously to Example 9:

25 (1) 3-Z-[1-(4-bromo-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone

Prepared from 3-Z-[1-(4-bromo-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

$R_f$  value: 0.4 (silica gel, toluene/ethyl acetate = 5:1)

$C_{22}H_{15}BrN_2O_3$

30 ESI mass spectrum:  $m/z = 435/437 [M+H^+]$

(2) 3-Z-[1-(3-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone

Prepared from 3-Z-[1-(3-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

5  $R_f$  value: 0.7 (Reversed phase RP 8, methanol/five percent saline solution = 4:1)

$C_{25}H_{23}N_3O_3$

ESI mass spectrum:  $m/z = 414 [M+H^+]$

10 (3) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone

Prepared from 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

$R_f$  value: 0.7 (Reversed phase RP 8, methanol/five percent saline solution = 4:1)

$C_{25}H_{23}N_3O_3$

15 ESI mass spectrum:  $m/z = 412 [M-H^-]$

(4) 3-Z-[1-(4-[(2,6-dimethyl-piperidin-1-yl)-methyl]-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone

20 Prepared from 3-Z-[1-(4-[(2,6-dimethyl-piperidin-1-yl)-methyl]-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

$R_f$  value: 0.6 (Reversed phase RP 8, methanol/five percent saline solution = 4:1)

$C_{30}H_{31}N_3O_3$

ESI mass spectrum:  $m/z = 482 [M+H^+]$

25 (5) 3-Z-[1-(4-(1-methyl-imidazol-2-yl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone

Prepared from 3-Z-[1-(4-(1-methyl-imidazol-2-yl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

$R_f$  value: 0.6 (Reversed phase RP 8, methanol/five percent saline solution = 4:1)

30  $C_{26}H_{20}N_4O_3$

ESI mass spectrum:  $m/z = 435 [M-H^-]$

(6) 3-Z-[1-(4-(N-acetyl-N-dimethylaminocarbonylmethyl-amino)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone

Prepared from 3-Z-[1-(4-(N-acetyl-N-dimethylaminocarbonylmethyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

$R_f$  value: 0.3 (silica gel, methylene chloride/methanol = 10:1)

$C_{28}H_{26}N_4O_5$

ESI mass spectrum:  $m/z = 497$   $[M-H^-]$

10 (7) 3-Z-[1-(4-ethylaminomethyl-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone

Prepared from 3-Z-[1-(4-ethylaminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

$R_f$  value: 0.6 (Reversed phase RP 8, methanol/five percent saline solution = 4:1)

$C_{25}H_{23}N_3O_3$

15 ESI mass spectrum:  $m/z = 412$   $[M-H^-]$

(8) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone

Prepared from 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

$R_f$  value: 0.6 (Reversed phase RP 8, methanol/five percent saline solution = 4:1)

$C_{27}H_{26}N_4O_4$

ESI mass spectrum:  $m/z = 469$   $[M-H^-]$

25 (9) 3-Z-[1-(4-(N-tert.butoxycarbonyl-ethylaminomethyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone

Prepared from 3-Z-[1-(4-(N-tert.butoxycarbonyl-ethylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

$R_f$  value: 0.4 (silica gel, methylene chloride/methanol = 10:1)

30  $C_{30}H_{31}N_3O_5$

ESI mass spectrum:  $m/z = 512$   $[M-H^-]$

(10) 3-Z-[1-(4-((N-carboxymethyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-((N-ethoxycarbonylmethyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl -2-indolinone

R<sub>f</sub> value: 0.4 (silica gel, methylene chloride/methanol = 6:1)

C<sub>27</sub>H<sub>25</sub>N<sub>3</sub>O<sub>5</sub>

ESI mass spectrum: m/z = 470 [M-H<sup>-</sup>]

#### Example 10

3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

---

0.9 g of 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone are suspended in 35 ml of dimethylformamide and 0.4 g of carbonyldiimidazole are added. The mixture is stirred for 14 hours at 80°C. After this time 20 ml of methanol are added and the mixture is stirred for another 3 hours at 50°C. The solvent is removed and the residue is purified over a silica gel column with methylene chloride/methanol (3:1) as eluant.

Yield: 0.5 g of (49% of theory),

R<sub>f</sub> value: 0.5 (aluminium oxide, methylene chloride/methanol = 30:1)

C<sub>29</sub>H<sub>29</sub>N<sub>3</sub>O<sub>3</sub>

ESI mass spectrum: m/z = 468 [M+H<sup>+</sup>]

The following compounds are prepared analogously to Example 10:

(1) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-benzyloxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone and benzyl alcohol

R<sub>f</sub> value: 0.6 (aluminium oxide, methylene chloride/methanol = 30:1)

C<sub>35</sub>H<sub>33</sub>N<sub>3</sub>O<sub>3</sub>

5 Mass spectrum: m/z = 543 [M<sup>+</sup>]

(2) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-isopropoxy-carbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone and isopropanol

R<sub>f</sub> value: 0.4 (aluminium oxide, methylene chloride/isopropanol = 30:1)

C<sub>31</sub>H<sub>33</sub>N<sub>3</sub>O<sub>3</sub>

Mass spectrum: m/z = 495 [M<sup>+</sup>]

(3) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-propyloxy-carbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone and n-propanol

R<sub>f</sub> value: 0.7 (silica gel, methylene chloride/methanol = 5:1)

C<sub>31</sub>H<sub>33</sub>N<sub>3</sub>O<sub>3</sub>

Mass spectrum: m/z = 495 [M<sup>+</sup>]

(4) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-butyloxy-carbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone and n-butanol

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 10:1)

C<sub>32</sub>H<sub>35</sub>N<sub>3</sub>O<sub>3</sub>

Mass spectrum: m/z = 509 [M<sup>+</sup>]

(5) 3-Z-[1-(4-bromo-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

Prepared from 3-Z-[1-(4-bromo-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone and ammonia

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 10:1)

5 C<sub>22</sub>H<sub>16</sub>BrN<sub>2</sub>O<sub>3</sub>

Mass spectrum: m/z = 432/434 [M-H<sup>-</sup>]

(6) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethylcarbamoyl-2-indolinone

10 Prepared from 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone and ethylamine gas

R<sub>f</sub> value: 0.6 (silica gel, methylene chloride/methanol = 5:1)

C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>2</sub>

Mass spectrum: m/z = 480 [M<sup>+</sup>]

15

(7) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-[(2-methoxy-ethoxy)-carbonyl]-2-indolinone

Prepared from 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone and methylglycol

20 R<sub>f</sub> value: 0.8 (silica gel, methylene chloride/methanol = 4:1)

C<sub>25</sub>H<sub>23</sub>N<sub>3</sub>O<sub>3</sub>

ESI mass spectrum: m/z = 470 [M-H<sup>-</sup>]

(8) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-[(2-dimethylamino-ethoxy)-carbonyl]-2-indolinone

25

Prepared from 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone and 2-dimethylaminoethanol aniline

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 5:2)

C<sub>29</sub>H<sub>32</sub>N<sub>4</sub>O<sub>3</sub>

30 ESI mass spectrum: m/z = 483 [M-H<sup>-</sup>]

(9) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-[(2-N-tert.butoxycarbonyl-amino-ethoxy)-carbonyl]-2-indolinone

Prepared from 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone and 2-N-tert.butoxycarbonyl-amino-ethanol aniline

5 R<sub>f</sub> value: 0.8 (silica gel, methylene chloride/methanol = 5:2)

C<sub>32</sub>H<sub>36</sub>N<sub>4</sub>O<sub>5</sub>

ESI mass spectrum: m/z = 412 [M-H<sup>-</sup>]

(10) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-[(2,2,2-trifluoroethoxy)-carbonyl]-2-indolinone

10

Prepared from 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone and 2,2,2-trifluoroethanol aniline

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 5:1)

C<sub>27</sub>H<sub>24</sub>F<sub>3</sub>N<sub>3</sub>O<sub>3</sub>

15 ESI mass spectrum: m/z = 494 [M-H<sup>-</sup>]

### Example 11

3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

20

0.9 g of 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone, 0.8 g of TBTU and 0.4 g of HOBT are suspended in 25 ml of dimethylformamide and 1.0 ml of triethylamine are added. The mixture is stirred for 15 minutes at room temperature. After this time ammonia gas is introduced at 10-15°C over a period of 15 minutes and the mixture is stirred for 1.5 hours at room temperature. The precipitate formed is suction filtered, washed with water, ethanol and ether and dried at 100°C *in vacuo*.

25

Yield: 0.6 g (64 % of theory),

R<sub>f</sub> value: 0.4 (Reversed phase RP 8, methanol/five percent saline solution = 6:4)

30 C<sub>28</sub>H<sub>28</sub>N<sub>4</sub>O<sub>2</sub>

ESI mass spectrum: m/z = 453 [M+H<sup>+</sup>]

The following compounds are prepared analogously to Example 11:

- 5 (1) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-dimethylcarbamoyl-2-indolinone

Prepared from 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone and dimethylamine hydrochloride/diisopropylethylamine

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol = 5:1)

C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>2</sub>

- 10 ESI mass spectrum: m/z = 481 [M+H<sup>+</sup>]

- (2) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-(N-ethyl-N-methylcarbamoyl)-2-indolinone

- 15 Prepared from 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone and N-ethyl-N-methyl-amine

R<sub>f</sub> value: 0.5 (aluminium oxide, methylene chloride/ethanol = 20:1)

C<sub>31</sub>H<sub>34</sub>N<sub>4</sub>O<sub>2</sub>

ESI mass spectrum: m/z = 495 [M+H<sup>+</sup>]

- 20 (3) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methylcarbamoyl-2-indolinone

Prepared from 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone and methylamine hydrochloride/diisopropylethylamine

R<sub>f</sub> value: 0.3 (aluminium oxide, methylene chloride/ethanol = 20:1)

- 25 C<sub>29</sub>H<sub>30</sub>N<sub>4</sub>O<sub>2</sub>

ESI mass spectrum: m/z = 467 [M+H<sup>+</sup>]

- (4) 3-Z-[1-(3-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-methylcarbamoyl-2-indolinone

- 30 Prepared from 3-Z-[1-(3-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-carboxyl-2-indolinone and methylamine hydrochloride/triethylamine



R<sub>f</sub> value: 0.3 (silica gel, methylene chloride/ethanol = 2:1)

C<sub>26</sub>H<sub>26</sub>N<sub>4</sub>O<sub>2</sub>

Mass spectrum: m/z = 426 [M<sup>+</sup>]

- 5 (5) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-(2-hydroxyethyl-carbamoyl)-2-indolinone

Prepared from 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone and ethanolamine/diisopropylethylamine

R<sub>f</sub> value: 0.5 (aluminium oxide, methylene chloride/methanol = 20:1)

- 10 C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>3</sub>

ESI mass spectrum: m/z = 495 [M-H<sup>-</sup>]

(6) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-diethylcarbamoyl-2-indolinone

- 15 Prepared from 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone and diethylamine hydrochloride/diisopropylethylamine

R<sub>f</sub> value: 0.8 (aluminium oxide, methylene chloride/methanol = 10:1)

C<sub>32</sub>H<sub>36</sub>N<sub>4</sub>O<sub>2</sub>

ESI mass spectrum: m/z = 509 [M+H<sup>+</sup>]

20

(7) 3-Z-[1-(4-(N-tert.butoxycarbonyl-ethylaminomethyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

Prepared from 3-Z-[1-(4-(N-tert.butoxycarbonyl-ethylaminomethyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone

- 25 R<sub>f</sub> value: 0.3 (silica gel, toluene/ethyl acetate/ethanol = 4:2:1)

C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>4</sub>

ESI mass spectrum: m/z = 511 [M-H<sup>-</sup>]

- 30 (8) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

Prepared from 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone

R<sub>f</sub> value: 0.5 (silica gel, methylene chloride/methanol/ammonia = 5:1:0.01)

5 C<sub>27</sub>H<sub>27</sub>N<sub>5</sub>O<sub>3</sub>

ESI mass spectrum: m/z = 468 [M-H<sup>-</sup>]

### Example 12

10 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone x citric acid

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3.25 g of citric acid monohydrate are placed in 50 ml of methanol and 5.0 g of 3-Z-[1-(4-(N-dimethylaminomethyl-carbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone are added at room temperature. The solution formed is evaporated down, the residue is washed with ether and recrystallised from ethyl acetate. Yield: 6.3 g (90 % of theory),

R<sub>f</sub> value: 0.6 (silica gel, methylene chloride/methanol/ammonia = 5:1:0.01)

Melting point: 198°C

20 C<sub>28</sub>H<sub>28</sub>N<sub>4</sub>O<sub>5</sub> x C<sub>6</sub>H<sub>8</sub>O<sub>7</sub>

ESI mass spectrum: m/z = 483 [M-H<sup>-</sup>]

Elemental analysis: calc.: C 60.34 H 5.37 N 8.28

found: 59.98 5.25 8.13

25 The following compound is prepared analogously to Example 12:

(1) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone x methanesulphonic acid

Prepared from 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-

30 methoxycarbonyl-2-indolinone and methanesulphonic acid

R<sub>f</sub> value: 0.6 (silica gel, methylene chloride/methanol/ammonia = 5:1:0.01)

Melting point: 275°C

$C_{26}H_{25}N_3O_3 \times CH_4O_3S$

ESI mass spectrum:  $m/z = 426 [M-H^-]$

Elemental analysis: calc.: C 61.92 H 5.59 N 8.03 S 6.12

5 found: 61.43 5.87 7.85 5.39

The following compounds may be prepared analogously to the foregoing Examples:

- 10 (1) 3-Z-(1-anilino-1-phenyl-methylene)-6-ethoxycarbonyl-2-indolinone
- (2) 3-Z-[1-(4-nitro-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
- (3) 3-Z-[1-(4-fluoro-anilino)-1-phenyl-methylene]-6-ethoxy-carbonyl-2-indolinone
- 15 (4) 3-Z-[1-(4-chloro-anilino)-1-phenyl-methylene]-6-ethoxy-carbonyl-2-indolinone
- (5) 3-Z-[1-(4-iodo-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
- (6) 3-Z-[1-(4-cyano-anilino)-1-phenyl-methylene]-6-ethoxy-carbonyl-2-indolinone
- 20 (7) 3-Z-[1-(4-methoxy-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
- (8) 3-Z-[1-(4-ethoxy-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
- 25 (9) 3-Z-[1-(4-trifluoromethyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
- (10) 3-Z-[1-(4-methyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
- 30 (11) 3-Z-[1-(4-methylmercapto-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(12) 3-Z-[1-(4-aminomethyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(13) 3-Z-[1-(4-(isopropylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-  
5 indolinone

(14) 3-Z-[1-(4-(anilinomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-  
indolinone

10 (15) 3-Z-[1-(4-(propylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-  
indolinone

(16) 3-Z-[1-(4-(butylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-  
indolinone

15 (17) 3-Z-[1-(4-(isobutylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-  
indolinone

(18) 3-Z-[1-(4-(cyclohexylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-  
20 2-indolinone

(19) 3-Z-[1-(4-(benzylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-  
indolinone

25 (20) 3-Z-[1-(4-((N-ethyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-  
ethoxycarbonyl-2-indolinone

(21) 3-Z-[1-(4-((N-methyl-N-propyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-  
ethoxycarbonyl-2-indolinone

30

(22) 3-Z-[1-(4-((N-isopropyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

5 (23) 3-Z-[1-(4-((N-ethyl-N-propyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(24) 3-Z-[1-(4-((N-ethyl-N-isopropyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

10 (25) 3-Z-[1-(4-(dipropylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(26) 3-Z-[1-(4-(diisopropylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

15 (27) 3-Z-[1-(4-((N-benzyl-N-ethyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

20 (28) 3-Z-[1-(4-(dibenzylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(29) 3-Z-[1-(4-(3,6-dihydro-2H-pyridin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

25 (30) 3-Z-[1-(4-(3,5-dimethyl-piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(31) 3-Z-[1-(4-(azepan-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

30

(32) 3-Z-[1-(4-(piperazin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

5 (33) 3-Z-[1-(4-(morpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(34) 3-Z-[1-(4-(thiomorpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

10 (35) 3-Z-[1-(4-(1-oxo-thiomorpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(36) 3-Z-[1-(4-(1,1-dioxo-thiomorpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

15 (37) 3-Z-[1-(4-(acetylamino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

20 (38) 3-Z-[1-(4-(2-amino-ethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(39) 3-Z-[1-(4-(2-methylamino-ethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

25 (40) 3-Z-[1-(4-(2-ethylamino-ethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(41) 3-Z-[1-(4-(2-diethylamino-ethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

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(42) 3-Z-[1-(4-(2-piperidin-1-yl-ethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(43) 3-Z-[1-(4-(2-acetylamino-ethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(44) 3-Z-[1-(4-(3-amino-propyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(45) 3-Z-[1-(4-(3-dimethylamino-propyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(46) 3-Z-[1-(4-(N-aminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(47) 3-Z-[1-(4-(N-methylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(48) 3-Z-[1-(4-(N-ethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(49) 3-Z-[1-(4-(N-diethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(50) 3-Z-[1-(4-(N-(piperidin-1-yl-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(51) 3-Z-[1-(4-(N-(morpholin-4-yl-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(52) 3-Z-[1-(4-(N-(piperazin-1-yl-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

5 (53) 3-Z-[1-(4-(N-(2-amino-ethylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(54) 3-Z-[1-(4-(N-(2-methylamino-ethylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

10 (55) 3-Z-[1-(4-(N-(2-diethylamino-ethylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(56) 3-Z-[1-(4-(N-acetyl-N-(2-aminoethyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

15 (57) 3-Z-[1-(4-(N-acetyl-N-(2-methylamino-ethyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

20 (58) 3-Z-[1-(4-(N-acetyl-N-(2-methylamino-propyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(59) 3-Z-[1-(4-(N-acetyl-N-(2-piperidin-1-yl-ethyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

25 (60) 3-Z-[1-(4-(N-acetyl-N-(aminocarbonylmethyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(61) 3-Z-[1-(4-(N-acetyl-N-(dimethylaminocarbonylmethyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

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(62) 3-Z-[1-(4-(N-acetyl-N-(piperidin-1-yl-carbonylmethyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

5 (63) 3-Z-[1-(4-(N-methyl-N-(aminocarbonyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(64) 3-Z-[1-(4-(N-methyl-N-(methylaminocarbonyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

10 (65) 3-Z-[1-(4-(N-methyl-N-(dimethylaminocarbonyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(66) 3-Z-[1-(4-(N-methyl-N-(piperidin-1-yl-carbonyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

15 (67) 3-Z-[1-(4-(N-(2-aminoethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(68) 3-Z-[1-(4-(N-(2-methylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

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(69) 3-Z-[1-(4-(N-(2-ethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

25 (70) 3-Z-[1-(4-(N-(2-diethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(71) 3-Z-[1-(4-(N-(2-pyrrolidin-1-yl-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

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(72) 3-Z-[1-(4-(N-(2-piperidin-1-yl-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(73) 3-Z-[1-(4-(N-(2-piperazin-1-yl-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(74) 3-Z-[1-(4-(N-(2-(morpholin-4-yl)-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(75) 3-Z-[1-(4-(N-(aminocarbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(76) 3-Z-[1-(4-(N-(methylaminocarbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(77) 3-Z-[1-(4-(N-(ethylaminocarbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(78) 3-Z-[1-(4-(N-(N-(2-dimethylamino-ethyl)-N-methyl-amino)-carbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(79) 3-Z-[1-(4-(N-(diethylaminocarbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(80) 3-Z-[1-(4-(N-(pyrrolidin-1-yl-carbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(81) 3-Z-[1-(4-(N-(piperidin-1-yl-carbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(82) 3-Z-[1-(4-(N-(piperazin-1-yl-carbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(83) 3-Z-[1-(4-(N-((morpholin-4-yl)-carbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(84) 3-Z-[1-(4-(2-dimethylamino-ethoxy)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(85) 3-Z-[1-(4-(3-dimethylamino-propoxy)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(86) 3-Z-[1-(4-(aminocarbonylmethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(87) 3-Z-[1-(4-(2-aminocarbonyl-ethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(88) 3-Z-[1-(4-(pyridin-2-yl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(89) 3-Z-[1-(4-(pyridine-3-yl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(90) 3-Z-[1-(4-(pyridin-4-yl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(91) 3-Z-[1-(4-(N-acetyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(92) 3-Z-[1-(4-(N-ethylcarbonyl-N-(dimethylaminocarbonyl-methyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(93) 3-Z-[1-(carbamoylmethyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

5 (94) 3-Z-[1-(4-dimethylcarbamoylmethyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(95) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-methylene]-6-ethoxycarbonyl-2-indolinone

10 (96) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-propylidene]-6-ethoxycarbonyl-2-indolinone

(97) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-butylidene]-6-ethoxycarbonyl-2-indolinone

15 (98) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-anilino)-methylene]-6-ethoxycarbonyl-2-indolinone

(99) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-anilino)-ethylidene]-6-ethoxycarbonyl-2-indolinone

20 (100) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-anilino)-propylidene]-6-ethoxycarbonyl-2-indolinone

(101) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-anilino)-butylidene]-6-ethoxycarbonyl-2-indolinone

25 (102) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-methylene]-6-ethoxycarbonyl-2-indolinone

30 (103) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-propylidene]-6-ethoxycarbonyl-2-indolinone

- (104) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-butylidene]-6-ethoxycarbonyl-2-indolinone
- (105) 3-Z-[1-(4-tetrazol-5-yl-anilino)-methylene]-6-ethoxycarbonyl-2-indolinone
- 5 (106) 3-Z-[1-(4-tetrazol-5-yl-anilino)-ethylidene]-6-ethoxycarbonyl-2-indolinone
- (107) 3-Z-[1-(4-tetrazol-5-yl-anilino)-propylidene]-6-ethoxycarbonyl-2-indolinone
- 10 (108) 3-Z-[1-(4-tetrazol-5-yl-anilino)-butylidene]-6-ethoxycarbonyl-2-indolinone
- (109) 3-Z-[1-(4-carboxy-anilino)-methylene]-6-ethoxycarbonyl-2-indolinone
- (110) 3-Z-[1-(4-carboxy-anilino)-propylidene]-6-ethoxycarbonyl-2-indolinone
- 15 (111) 3-Z-[1-(4-carboxy-anilino)-butylidene]-6-ethoxycarbonyl-2-indolinone
- (112) 3-Z-[1-(4-(N-(3-dimethylamino-propionyl)-N-dimethylaminocarbonylmethyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
- 20 (113) 3-Z-[1-(4-(N-(4-dimethylamino-butyryl)-N-dimethylaminocarbonylmethyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
- (114) 3-Z-[1-(4-(N-dimethylaminocarbonylmethyl-N-(2-dimethylamino-ethylsulphonyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
- 25 (115) 3-Z-[1-(4-(N-dimethylaminocarbonylmethyl-N-(3-dimethylamino-propylsulphonyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
- 30 (116) 3-Z-[1-(4-((2-hydroxy-ethyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(117) 3-Z-[1-(4-((2-methoxy-ethyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

5 (118) 3-Z-[1-(4-((2-dimethylamino-ethyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(119) 3-Z-[1-(4-((3-dimethylamino-propyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

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(120) 3-Z-[1-(4-((N-tert.butoxycarbonyl-2-amino-ethyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

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(121) 3-Z-[1-(4-((N-tert.butoxycarbonyl-3-amino-propyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(122) 3-Z-[1-(4-((2-amino-ethyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

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(123) 3-Z-[1-(4-((3-amino-propyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(124) 3-Z-[1-(4-((2-acetylamino-ethyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

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(125) 3-Z-[1-(4-((3-acetylamino-propyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

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(126) 3-Z-[1-(4-((2-methylsulphonylamino-ethyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(127) 3-Z-[1-(4-((3-methylsulphonylamino-propyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

5 (128) 3-Z-[1-(4-(N-(N-tert.butoxycarbonyl-2-amino-ethyl)-N-methyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(129) 3-Z-[1-(4-(N-(2-amino-ethyl)-N-methyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

10 (130) 3-Z-[1-(4-(N-(2-acetylamino-ethyl)-N-methyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(131) 3-Z-[1-(4-(N-(2-methylsulphonylamino-ethyl)-N-methyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

15 (132) 3-Z-[1-(4-(carboxymethyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

20 (133) 3-Z-[1-(4-(ethoxycarbonylmethyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(134) 3-Z-[1-(4-(carbamoylmethyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

25 (135) 3-Z-[1-(4-(dimethylcarbamoyl-methyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(136) 3-Z-[1-(4-(methylcarbamoyl-methyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

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(137) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-amino-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(138) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-nitro-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(139) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-acetyl-amino-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(140) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-methylsulphonylamino-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(141) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-cyano-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(142) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-hydroxy-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(143) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-methoxy-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(144) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-ethoxycarbonyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(145) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-carboxy-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(146) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-carbamoyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone



(147) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-chloro-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

5 (148) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-fluoro-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(149) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-bromo-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

10 (150) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-methyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(151) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-trifluoromethyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

15 (152) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3,5-dibromo-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

20 (153) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3,5-dichloro-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(154) 3-Z-[1-(4-(dimethylaminomethyl)-3-amino-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

25 (155) 3-Z-[1-(4-(dimethylaminomethyl)-3-nitro-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(156) 3-Z-[1-(4-(dimethylaminomethyl)-3-acetyl-amino-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

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(157) 3-Z-[1-(4-(dimethylaminomethyl)-3-(methylsulphonylamino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(158) 3-Z-[1-(4-(dimethylaminomethyl)-3-cyano-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(159) 3-Z-[1-(4-(dimethylaminomethyl)-3-hydroxy-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(160) 3-Z-[1-(4-(dimethylaminomethyl)-3-methoxy-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(161) 3-Z-[1-(4-(dimethylaminomethyl)-3-(ethoxycarbonyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(162) 3-Z-[1-(4-(dimethylaminomethyl)-3-carboxy-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(163) 3-Z-[1-(4-(dimethylaminomethyl)-3-carbamoyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(164) 3-Z-[1-(4-(dimethylaminomethyl)-3-chloro-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(165) 3-Z-[1-(4-(dimethylaminomethyl)-3-fluoro-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(166) 3-Z-[1-(4-(dimethylaminomethyl)-3-bromo-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(167) 3-Z-[1-(4-(dimethylaminomethyl)-3-methyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(168) 3-Z-[1-(4-(dimethylaminomethyl)-3-trifluoromethyl-anilino)-1-phenyl-methylene]-  
5 6-ethoxycarbonyl-2-indolinone

(169) 3-Z-[1-(4-(dimethylaminomethyl)-3,5-dibromo-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

10 (170) 3-Z-[1-(4-(dimethylaminomethyl)-3,5-dichloro-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(171) 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

15 (172) 3-Z-[1-(4-(N-(imidazo-1-yl-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(173) 3-Z-[1-(4-(N-(phthalimido-2-yl-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone  
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(174) 3-Z-[1-(4-(N-aminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

25 (175) 3-Z-[1-(4-(N-acetylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(176) 3-Z-[1-(4-(N-methylsulphonylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

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(177) 3-Z-[1-(4-(N-((N-(2-methoxyethyl)-N-methyl-amino)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(178) 3-Z-[1-(4-(N-((N-(2-dimethylaminoethyl)-N-methyl-amino)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(179) 3-Z-[1-(4-(N-((di-(2-hydroxyethyl)-amino)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(180) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-methylene]-6-ethoxycarbonyl-2-indolinone

(181) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-ethylidene]-6-ethoxycarbonyl-2-indolinone

(182) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-propylidene]-6-ethoxycarbonyl-2-indolinone

(183) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-butylidene]-6-ethoxycarbonyl-2-indolinone

(184) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-methylene]-6-ethoxycarbonyl-2-indolinone

(185) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-ethylidene]-6-ethoxycarbonyl-2-indolinone

(186) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-propylidene]-6-ethoxycarbonyl-2-indolinone

(187) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-butylidene]-6-ethoxycarbonyl-2-indolinone

(188) 3-Z-[1-(4-(N-dimethylaminocarbonylmethyl-amino)-anilino)-1-phenyl-methylene]-  
5 6-ethoxycarbonyl-2-indolinone

(189) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

10 (190) 3-Z-[1-(4-((imidazolidin-2,4-dion-5-ylidene)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(191) 3-Z-[1-(4-(N-((2-dimethylamino-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

15 (192) 3-Z-[1-(4-(N-tert.butoxycarbonyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(193) 3-Z-[1-(4-(2-oxo-pyrrolidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-  
20 ethoxycarbonyl-2-indolinone

(194) 3-Z-[1-(4-(N-aminocarbonylmethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

25 (195) 3-Z-[1-(4-(N-cyanomethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(196) 3-Z-[1-(4-(2-(imidazol-4-yl)-ethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-  
2-indolinone

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(197) 3-Z-[1-(4-((2-(N-benzyl-N-methyl-amino)-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

5 (198) 3-Z-[1-(4-cyclohexylamino-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(199) 3-Z-[1-(4-(imidazol-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

10 (200) 3-Z-[1-(4-(imidazol-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(201) 3-Z-[1-(N-methyl-piperidine-4-yl-amino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

15 (202) 3-Z-[1-(4-(imidazol-4-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

20 (203) 3-Z-[1-(4-((4-hydroxy-piperidin-1-yl)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(204) 3-Z-[1-(4-((4-methoxy-piperidin-1-yl)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

25 (205) 3-Z-[1-(4-benzyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(206) 3-Z-[1-(4-(N-(3-trifluoroacetyl-amino-propyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

30 (207) 3-Z-[1-(4-(4-tert.butoxycarbonyl-piperazin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(208) 3-Z-[1-(4-(1-methyl-imidazol-2-yl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

5 (209) 3-Z-[1-(4-(1-methyl-imidazol-2-yl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(210) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-3-amino-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

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(211) 3-Z-[1-(4-((3-(N-benzyl-N-methyl-amino)-propyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

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(212) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(213) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-butyryl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

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(214) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-isobutyryl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(215) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-benzoyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

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(216) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-3-amino-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(217) 3-Z-[1-(4-(4-hydroxymethyl-piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

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(218) 3-Z-[1-(4-(2-(4-hydroxy-piperidin-1-yl)-ethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(219) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-propylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(220) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-butylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(221) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-phenylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(222) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-benzylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(223) 3-Z-[1-(4-((imidazolidin-2,4-dion-5-yl)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(224) 3-Z-[1-(4-((3-hydroxy-pyrrolidin-1-yl)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(225) 3-Z-[1-(4-(cyclohexyl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(226) 3-Z-[1-(4-(cyclohexyl-carbonyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(227) 3-Z-[1-(4-diethylaminomethyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone



(228) 3-Z-[1-(4-(N-(n-hexyl)-N-methyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(229) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-(furan-2-carbonyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(230) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-(2-methoxy-benzoyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(231) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-(pyridine-3-carbonyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(232) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-(phenyl-acetyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(233) 3-Z-[1-(4-(imidazol-2-yl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(234) 3-Z-[1-(4-(1-ethyl-imidazol-2-yl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(235) 3-Z-[1-(4-(1-benzyl-imidazol-2-yl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(236) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-isopropylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(237) 3-Z-[1-(4-(N-((4-benzyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(238) 3-Z-[1-(4-(N-(pyrrolidin-1-yl-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

5 (239) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-3-bromo-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(240) 3-Z-[1-(4-(5-methyl-imidazol-4-yl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

10 (241) 3-Z-[1-(4-(N-((2-dimethylamino-ethyl)-carbonyl)-N-isopropyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(242) 3-Z-[1-(4-(N-((2-dimethylamino-ethyl)-carbonyl)-N-benzyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

15 (243) 3-Z-[1-(4-(N-butyl-N-tert.butoxycarbonyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

20 (244) 3-Z-[1-(4-(N-((N-aminocarbonylmethyl-N-methyl-amino)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(245) 3-Z-[1-(4-(N-((N-benzyl-N-methyl-amino)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

25 (246) 3-Z-[1-(4-(N-(di-(2-methoxyethyl)-amino-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(247) 3-Z-[1-(4-(N-((2-(4-tert.butoxycarbonyl-piperazin-1-yl)-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

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(248) 3-Z-[1-(4-(N-((2-(piperidin-1-yl)-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

5 (249) 3-Z-[1-(4-(N-((2-(N-benzyl-N-methyl-amino)-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(250) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-isopropyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

10 (251) 3-Z-[1-(4-(N-(piperidin-1-yl-methylcarbonyl)-N-isopropyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(252) 3-Z-[1-(4-(N-((4-tert.butoxycarbonyl-piperazin-1-yl)-methylcarbonyl)-N-isopropyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

15 (253) 3-Z-[1-(4-(N-((N-benzyl-N-methyl-amino)-methylcarbonyl)-N-benzyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

20 (254) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-benzyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(255) 3-Z-[1-(4-(N-(piperidin-1-yl-methylcarbonyl)-N-benzyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

25 (256) 3-Z-[1-(4-(1,2,4-triazol-2-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(257) 3-Z-[1-(4-(1,2,3-triazol-2-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

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(258) 3-Z-[1-(4-(1,2,3-triazol-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

5 (259) 3-Z-[1-(4-((N-aminocarbonylmethyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(260) 3-Z-[1-(4-((di-(2-methoxy-ethyl)-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

10 (261) 3-Z-[1-(4-((di-(2-hydroxy-ethyl)-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(262) 3-Z-[1-(4-((N-ethoxycarbonylmethyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

15 (263) 3-Z-[1-(4-(azetidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(264) 3-Z-[1-(4-(N-propyl-N-tert.butoxycarbonyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(265) 3-Z-[1-(4-((N-(2-(2-methoxy-ethoxy)-ethyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

25 (266) 3-Z-[1-(4-((N-(tert.butoxycarbonyl-3-amino-propyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(267) 3-Z-[1-(4-((N-(methylcarbamoyl-methyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

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(268) 3-Z-[1-(4-((N-(dimethylcarbamoyl-methyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(269) 3-Z-[1-(4-((N-propyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(270) 3-Z-[1-(4-((N-(2-dimethylamino-ethyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(271) 3-Z-[1-(4-((N-(3-dimethylamino-propyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(272) 3-Z-[1-(4-((N-(2-methoxy-ethyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(273) 3-Z-[1-(4-((N-(2-hydroxy-ethyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(274) 3-Z-[1-(4-((N-(dioxolan-2-yl-methyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(275) 3-Z-[1-(4-(3-oxo-piperazin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(276) 3-Z-[1-(4-(N-(piperazin-1-yl-methylcarbonyl)-N-isopropyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(277) 3-Z-[1-(4-(N-((2-(piperazin-1-yl)-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(278) 3-Z-[1-(4-((N-(3-amino-propyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(279) 3-Z-[1-(4-(N-(3-methylamino-propyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(280) 3-Z-[1-(4-Ureidomethyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(281) 3-Z-[1-(4-guanidinomethyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(282) 3-Z-[1-(4-(N-methylsulphonyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(283) 3-Z-[1-(4-(4-benzoyl-piperazin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(284) 3-Z-[1-(4-((N-(3-acetylamino-propyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(285) 3-Z-[1-(4-((N-(3-methylsulphonylamino-propyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(286) 3-Z-[1-(4-((N-carboxymethyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(287) 3-Z-(1-anilino-1-phenyl-methylene)-6-methoxycarbonyl-2-indolinone

(288) 3-Z-[1-(4-nitro-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(289) 3-Z-[1-(4-fluoro-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(290) 3-Z-[1-(4-chloro-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

5 (291) 3-Z-[1-(4-bromo-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(292) 3-Z-[1-(4-iodo-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(293) 3-Z-[1-(4-cyano-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

10

(294) 3-Z-[1-(4-carboxy-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(295) 3-Z-[1-(4-methoxy-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

15 (296) 3-Z-[1-(4-ethoxy-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(297) 3-Z-[1-(4-trifluoromethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

20 (298) 3-Z-[1-(4-methylmercapto-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(299) 3-Z-[1-(4-(isopropylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

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(300) 3-Z-[1-(4-(anilinomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(301) 3-Z-[1-(4-(isobutylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

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(302) 3-Z-[1-(4-(cyclohexylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

5 (303) 3-Z-[1-(4-(benzylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(304) 3-Z-[1-(4-((N-methyl-N-propyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

10 (305) 3-Z-[1-(4-((N-isopropyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(306) 3-Z-[1-(4-((N-ethyl-N-propyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

15 (307) 3-Z-[1-(4-((N-ethyl-N-isopropyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

20 (308) 3-Z-[1-(4-(dipropylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(309) 3-Z-[1-(4-(diisopropylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

25 (310) 3-Z-[1-(4-((N-benzyl-N-ethyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(311) 3-Z-[1-(4-(dibenzylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

30



(312) 3-Z-[1-(4-(3,6-dihydro-2H-pyridin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(313) 3-Z-[1-(4-(3,5-dimethyl-piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(314) 3-Z-[1-(4-(azepan-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(315) 3-Z-[1-(4-(2-amino-ethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(316) 3-Z-[1-(4-(2-methylamino-ethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(317) 3-Z-[1-(4-(2-ethylamino-ethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(318) 3-Z-[1-(4-(2-dimethylamino-ethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(319) 3-Z-[1-(4-(2-diethylamino-ethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(320) 3-Z-[1-(4-(2-piperidin-1-yl-ethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(321) 3-Z-[1-(4-(2-acetylamino-ethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(322) 3-Z-[1-(4-(3-amino-propyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(323) 3-Z-[1-(4-(3-dimethylamino-propyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(324) 3-Z-[1-(4-(N-aminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(325) 3-Z-[1-(4-(N-ethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(326) 3-Z-[1-(4-(N-diethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(327) 3-Z-[1-(4-(N-dipropylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(328) 3-Z-[1-(4-(N-((N-ethyl-N-methyl-amino)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(329) 3-Z-[1-(4-(N-((N-ethyl-N-propyl-amino)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(330) 3-Z-[1-(4-(N-((N-methyl-N-propyl-amino)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(331) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-ethyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(332) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-propyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(333) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-butyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(334) 3-Z-[1-(4-(N-(2-amino-ethylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(335) 3-Z-[1-(4-(N-(2-diethylamino-ethylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(336) 3-Z-[1-(4-(N-acetyl-N-(2-aminoethyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(337) 3-Z-[1-(4-(N-acetyl-N-(2-methylamino-ethyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(338) 3-Z-[1-(4-(N-acetyl-N-(3-methylamino-propyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(339) 3-Z-[1-(4-(N-acetyl-N-(2-piperidin-1-yl-ethyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(340) 3-Z-[1-(4-(N-acetyl-N-(aminocarbonylmethyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(341) 3-Z-[1-(4-(N-acetyl-N-(piperidin-1-yl-carbonylmethyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(342) 3-Z-[1-(4-(N-methyl-N-(aminocarbonyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(343) 3-Z-[1-(4-(N-methyl-N-(methyaminocarbonyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(344) 3-Z-[1-(4-(N-methyl-N-(dimethylaminocarbonyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(345) 3-Z-[1-(4-(N-methyl-N-(piperidin-1-yl-carbonyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(346) 3-Z-[1-(4-(N-(2-ethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(347) 3-Z-[1-(4-(N-(2-diethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(348) 3-Z-[1-(4-(N-(2-pyrrolidin-1-yl-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(349) 3-Z-[1-(4-(N-(2-piperidin-1-yl-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(350) 3-Z-[1-(4-(N-(2-piperazin-1-yl-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(351) 3-Z-[1-(4-(N-(2-(4-morpholin-1-yl)-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(352) 3-Z-[1-(4-(N-(ethylaminocarbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(353) 3-Z-[1-(4-(N-(diethylaminocarbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(354) 3-Z-[1-(4-(N-(pyrrolidin-1-yl-carbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(355) 3-Z-[1-(4-(N-(piperidin-1-yl-carbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(356) 3-Z-[1-(4-(N-(piperazin-1-yl-carbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(357) 3-Z-[1-(4-(N-((morpholin-4-yl)-carbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(358) 3-Z-[1-(4-(2-dimethylamino-ethoxy)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(359) 3-Z-[1-(4-(3-dimethylamino-propoxy)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(360) 3-Z-[1-(4-(aminocarbonylmethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(361) 3-Z-[1-(4-(2-aminocarbonyl-ethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(362) 3-Z-[1-(4-(pyridin-2-yl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(363) 3-Z-[1-(4-(pyridine-3-yl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(364) 3-Z-[1-(4((N-phenethyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(365) 3-Z-[1-(4-(N-acetyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(366) 3-Z-[1-(4-(N-ethylcarbonyl-N-(dimethylaminocarbonyl-methyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(367) 3-Z-[1-(4-(N-methyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(368) 3-Z-[1-(4-carboxymethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(369) 3-Z-[1-(4-carbamoylmethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(370) 3-Z-[1-(4-dimethylcarbamoylmethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(371) 3-Z-[1-(4-tetrazol-5-yl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(372) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-methylene]-6-methoxycarbonyl-2-indolinone

5 (373) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-ethylidene]-6-methoxycarbonyl-2-indolinone

(374) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-propylidene]-6-methoxycarbonyl-2-indolinone

10 (375) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-butylidene]-6-methoxycarbonyl-2-indolinone

(376) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-anilino)-methylene]-6-methoxycarbonyl-2-indolinone

15 (377) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-anilino)-ethylidene]-6-methoxycarbonyl-2-indolinone

20 (378) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-anilino)-propylidene]-6-methoxycarbonyl-2-indolinone

(379) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-anilino)-butylidene]-6-methoxycarbonyl-2-indolinone

25 (380) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-methylene]-6-methoxycarbonyl-2-indolinone

(381) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-ethylidene]-6-methoxycarbonyl-2-indolinone

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(382) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-propylidene]-6-methoxycarbonyl-2-indolinone

(383) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-butylidene]-6-methoxycarbonyl-2-indolinone

(384) 3-Z-[1-(4-tetrazol-5-yl-anilino)-methylene]-6-methoxycarbonyl-2-indolinone

(385) 3-Z-[1-(4-tetrazol-5-yl-anilino)-ethylidene]-6-methoxycarbonyl-2-indolinone

(386) 3-Z-[1-(4-tetrazol-5-yl-anilino)-propylidene]-6-methoxycarbonyl-2-indolinone

(387) 3-Z-[1-(4-tetrazol-5-yl-anilino)-butylidene]-6-methoxycarbonyl-2-indolinone

(388) 3-Z-[1-(4-carboxy-anilino)-methylene]-6-methoxycarbonyl-2-indolinone

(389) 3-Z-[1-(4-carboxy-anilino)-ethylidene]-6-methoxycarbonyl-2-indolinone

(390) 3-Z-[1-(4-carboxy-anilino)-propylidene]-6-methoxy-carbonyl-2-indolinone

(391) 3-Z-[1-(4-carboxy-anilino)-butylidene]-6-methoxycarbonyl-2-indolinone

(392) 3-Z-[1-(4-(N-benzyl-N-methyl-aminomethyl)-anilino)-1-methyl-methylene]-6-methoxycarbonyl-2-indolinone

(393) 3-Z-[1-(4-(2,3,4,5-tetrahydro-benzo(d)azepin-3-yl-methyl)-anilino)-1-methyl-methylene]-6-methoxycarbonyl-2-indolinone

(394) 3-Z-[1-(4-((benzo(1,3)dioxol-5-yl-methyl)-methyl-amino-methyl)-anilino)-1-methyl-methylene]-6-methoxycarbonyl-2-indolinone



(395) 3-Z-[1-(4-(N-phenethyl-N-methyl-aminomethyl)-anilino)-1-methyl-methylene]-6-methoxycarbonyl-2-indolinone

(396) 3-Z-[1-(4-(N-(3,4-dimethoxy-benzyl)-N-methyl-amino-methyl)-anilino)-1-methyl-methylene]-6-methoxycarbonyl-2-indolinone

(397) 3-Z-[1-(4-(N-(4-Chloro-benzyl)-N-methyl-amino-methyl)-anilino)-1-methyl-methylene]-6-methoxycarbonyl-2-indolinone

(398) 3-Z-[1-(4-(N-(4-methylbenzyl)-N-methyl-amino-methyl)-anilino)-1-methyl-methylene]-6-methoxycarbonyl-2-indolinone

(399) 3-Z-[1-(4-(N-(4-fluoro-benzyl)-N-methyl-amino-methyl)-anilino)-1-methyl-methylene]-6-methoxycarbonyl-2-indolinone

(400) 3-Z-[1-(4-(N-(4-bromo-benzyl)-N-methyl-amino-methyl)-anilino)-1-methyl-methylene]-6-methoxycarbonyl-2-indolinone

(401) 3-Z-[1-(4-(N-(3-dimethylamino-propionyl)-N-dimethylaminocarbonylmethyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(402) 3-Z-[1-(4-(N-(4-dimethylamino-butyryl)-N-dimethylaminocarbonylmethyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(403) 3-Z-[1-(4-(N-dimethylaminocarbonylmethyl-N-(2-dimethylamino-ethylsulphonyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(404) 3-Z-[1-(4-(N-dimethylaminocarbonylmethyl-N-(3-dimethylamino-propylsulphonyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(405) 3-Z-[1-(4-((2-hydroxy-ethyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

5 (406) 3-Z-[1-(4-((2-methoxy-ethyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(407) 3-Z-[1-(4-((2-dimethylamino-ethyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

10 (408) 3-Z-[1-(4-((3-dimethylamino-propyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(409) 3-Z-[1-(4-((N-tert.butoxycarbonyl-2-amino-ethyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

15 (410) 3-Z-[1-(4-((N-tert.butoxycarbonyl-3-amino-propyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

20 (411) 3-Z-[1-(4-((2-amino-ethyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(412) 3-Z-[1-(4-((3-amino-propyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

25 (413) 3-Z-[1-(4-((2-acetylamino-ethyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(414) 3-Z-[1-(4-((3-acetylamino-propyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

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(415) 3-Z-[1-(4-((2-methylsulphonylamino-ethyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(416) 3-Z-[1-(4-((3-methylsulphonylamino-propyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(417) 3-Z-[1-(4-(N-(N-tert.butoxycarbonyl-2-amino-ethyl)-N-methyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(418) 3-Z-[1-(4-(N-(2-amino-ethyl)-N-methyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(419) 3-Z-[1-(4-(N-(2-acetylamino-ethyl)-N-methyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(420) 3-Z-[1-(4-(N-(2-methylsulphonylamino-ethyl)-N-methyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(421) 3-Z-[1-(4-(carboxymethyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(422) 3-Z-[1-(4-(ethoxycarbonylmethyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(423) 3-Z-[1-(4-(carbamoylmethyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(424) 3-Z-[1-(4-(dimethylcarbamoyl-methyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(425) 3-Z-[1-(4-(methylcarbamoyl-methyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(426) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-amino-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(427) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-nitro-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(428) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-acetyl-amino-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(429) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-methylsulphonylamino-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(430) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-cyano-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(431) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-hydroxy-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(432) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-methoxy-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(433) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-ethoxycarbonyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(434) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-carboxy-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(435) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-carbamoyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(436) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-chloro-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(437) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-fluoro-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(438) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-bromo-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(439) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-methyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(440) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-trifluoromethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(441) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3,5-dibromo-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(442) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3,5-dichloro-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(443) 3-Z-[1-(4-(dimethylaminomethyl)-3-amino-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(444) 3-Z-[1-(4-(dimethylaminomethyl)-3-nitro-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(445) 3-Z-[1-(4-(dimethylaminomethyl)-3-acetylamino-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

5 (446) 3-Z-[1-(4-(dimethylaminomethyl)-3-methylsulphonylamino-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(447) 3-Z-[1-(4-(dimethylaminomethyl)-3-cyano-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

10 (448) 3-Z-[1-(4-(dimethylaminomethyl)-3-hydroxy-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(449) 3-Z-[1-(4-(dimethylaminomethyl)-3-methoxy-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

15 (450) 3-Z-[1-(4-(dimethylaminomethyl)-3-ethoxycarbonyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

20 (451) 3-Z-[1-(4-(dimethylaminomethyl)-3-carboxy-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(452) 3-Z-[1-(4-(dimethylaminomethyl)-3-carbamoyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

25 (453) 3-Z-[1-(4-(dimethylaminomethyl)-3-chloro-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(454) 3-Z-[1-(4-(dimethylaminomethyl)-3-fluoro-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

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(455) 3-Z-[1-(4-(dimethylaminomethyl)-3-bromo-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

5 (456) 3-Z-[1-(4-(dimethylaminomethyl)-3-methyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(457) 3-Z-[1-(4-(dimethylaminomethyl)-3-trifluoromethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

10 (458) 3-Z-[1-(4-dimethylaminomethyl-3,5-dibromo-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(459) 3-Z-[1-(4-(dimethylaminomethyl)-3,5-dichloro-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

15 (460) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-[(2-hydroxy-ethoxy)-carbonyl]-2-indolinone

20 (461) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-[(ethoxycarbonyl-methoxy)-carbonyl]-2-indolinone

(462) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-[(carboxy-methoxy)-carbonyl]-2-indolinone

25 (463) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-[(carbamoyl-methoxy)-carbonyl]-2-indolinone

(464) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-[(2-hydroxy-ethoxy)-carbonyl]-2-indolinone

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(465) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-[(ethoxycarbonyl-methoxy)-carbonyl]-2-indolinone

(466) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-[(carboxy-methoxy)-carbonyl]-2-indolinone

(467) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-[(carbamoyl-methoxy)-carbonyl]-2-indolinone

(468) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-[(2-methoxy-ethoxy)-carbonyl]-2-indolinone

(469) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-[(2-dimethylamino-ethoxy)-carbonyl]-2-indolinone

(470) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-[(2-(N-tert.butoxycarbonyl-amino)-ethoxy)-carbonyl]-2-indolinone

(471) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-[(2-amino-ethoxy)-carbonyl]-2-indolinone

(472) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-[(2,2,2-trifluoroethoxy)-carbonyl]-2-indolinone

(473) 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(474) 3-Z-[1-(4-(N-(imidazo-1-yl-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone



(475) 3-Z-[1-(4-(N-(phthalimido-2-yl-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

5 (476) 3-Z-[1-(4-(N-aminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(477) 3-Z-[1-(4-(N-acetylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

10 (478) 3-Z-[1-(4-(N-methylsulphonylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(479) 3-Z-[1-(4-(N-((N-(2-methoxyethyl)-N-methyl-amino)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

15 (480) 3-Z-[1-(4-(N-((N-(2-dimethylaminoethyl)-N-methyl-amino)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

20 (481) 3-Z-[1-(4-(N-((di-(2-hydroxyethyl)-amino)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(482) 3-Z-[1-(4-tert.butoxycarbonylmethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

25 (483) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-methylene]-6-methoxycarbonyl-2-indolinone

(484) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-ethylidene]-6-methoxycarbonyl-2-indolinone

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(485) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-propylidene]-6-methoxycarbonyl-2-indolinone

5 (486) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-butylidene]-6-methoxycarbonyl-2-indolinone

(487) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-methylene]-6-methoxycarbonyl-2-indolinone

10 (488) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-ethylidene]-6-methoxycarbonyl-2-indolinone

(489) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-propylidene]-6-methoxycarbonyl-2-indolinone

15 (490) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-butylidene]-6-methoxycarbonyl-2-indolinone

20 (491) 3-Z-[1-(4-tert.butylloxycarbonyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(492) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

25 (493) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(494) 3-Z-[1-(4-(N-methyl-acetyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

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(495) 3-Z-[1-(4-(imidazol-4-yl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(496) 3-Z-[1-(4-((N-(dioxolan-2-yl-methyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(497) 3-Z-[1-(4-(N-benzyl-N-methyl-amino-methyl)-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone

(498) 3-Z-[1-(4-(2,3,4,5-tetrahydro-benzo(d)azepin-3-yl-methyl)-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone

(499) 3-Z-[1-(4-((benzo(1,3)dioxol-5-yl-methyl)-methyl-amino-methyl)-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone

(500) 3-Z-[1-(4-(N-phenethyl-N-methyl-amino-methyl)-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone

(501) 3-Z-[1-(4-(N-(3,4-dimethoxy-benzyl)-N-methyl-amino-methyl)-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone

(502) 3-Z-[1-(4-(N-(4-Chloro-benzyl)-N-methyl-amino-methyl)-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone

(503) 3-Z-[1-(4-(N-(4-methyl-benzyl)-N-methyl-amino-methyl)-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone

(504) 3-Z-[1-(4-(N-(4-fluoro-benzyl)-N-methyl-amino-methyl)-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone

(505) 3-Z-[1-(4-(N-(4-bromo-benzyl)-N-methyl-amino-methyl)-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone

(506) 3-Z-[1-(4-((N-(2-methoxy-ethyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(507) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-[(2-amino-ethoxy)-carbonyl]-2-indolinone

(508) 3-Z-[1-(4-((N-(3-methylsulfonylamino-propyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

### Example 13

Dry ampoule containing 75 mg of active substance per 10 ml

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#### Composition:

Active substance	75.0 mg
Mannitol	50.0 mg
water for injection	ad 10.0 ml

#### Preparation:

Active substance and mannitol are dissolved in water. After packaging the solution is freeze-dried. To produce the solution ready for use, the product is dissolved in water for injections.

### Example 14

Dry ampoule containing 35 mg of active substance per 2 ml

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Composition:

	Active substance	35.0 mg
	Mannitol	100.0 mg
5	water for injections	ad 2.0 ml

Preparation:

Active substance and mannitol are dissolved in water. After packaging, the solution is freeze-dried.

10

To produce the solution ready for use, the product is dissolved in water for injections.

Example 15

15    Tablet containing 50 mg of active substance

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Composition:

	(1) Active substance	50.0 mg
20	(2) Lactose	98.0 mg
	(3) Maize starch	50.0 mg
	(4) Polyvinylpyrrolidone	15.0 mg
	(5) Magnesium stearate	<u>2.0 mg</u>
		215.0 mg

25

Preparation:

(1), (2) and (3) are mixed together and granulated with an aqueous solution of (4). (5) is added to the dried granulated material. From this mixture tablets are pressed, biplanar, faceted on both sides and with a dividing notch on one side.

30    Diameter of the tablets: 9 mm.

Example 16

Tablet containing 350 mg of active substance

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5      Composition:

	(1) Active substance	350.0 mg
	(2) Lactose	136.0 mg
	(3) Maize starch	80.0 mg
10	(4) Polyvinylpyrrolidone	30.0 mg
	(5) Magnesium stearate	<u>4.0 mg</u>
		600.0 mg

Preparation:

- 15      (1), (2) and (3) are mixed together and granulated with an aqueous solution of (4). (5) is added to the dried granulated material. From this mixture tablets are pressed, biplanar, faceted on both sides and with a dividing notch on one side.

Diameter of the tablets: 12 mm.

20      Example 17

Capsules containing 50 mg of active substance

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Composition:

25	(1) Active substance	50.0 mg
	(2) Dried maize starch	58.0 mg
	(3) Powdered lactose	50.0 mg
	(4) Magnesium stearate	<u>2.0 mg</u>
30		160.0 mg

Preparation:

(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing.

- 5 This powder mixture is packed into size 3 hard gelatine capsules in a capsule filling machine.

Example 18

- 10 Capsules containing 350 mg of active substance
- 

Composition:

- |    |                        |               |
|----|------------------------|---------------|
|    | (1) Active substance   | 350.0 mg      |
| 15 | (2) Dried maize starch | 46.0 mg       |
|    | (3) Powdered lactose   | 30.0 mg       |
|    | (4) Magnesium stearate | <u>4.0 mg</u> |
|    |                        | 430.0 mg      |

- 20 Preparation:

(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing.

- 25 This powder mixture is packed into size 0 hard gelatine capsules in a capsule filling machine.

Example 19

Suppositories containing 100 mg of active substance

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1 suppository contains:

Active substance	100.0 mg
Polyethyleneglycol (M.W. 1500)	600.0 mg
Polyethyleneglycol (M.W. 6000)	460.0 mg
Polyethylenesorbitan monostearate	<u>840.0 mg</u>
5	2,000.0 mg

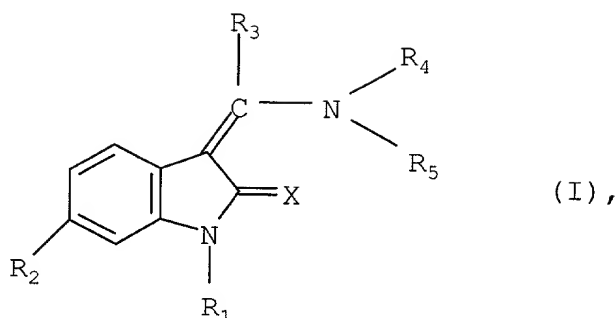
Preparation:

The polyethyleneglycol is melted together with polyethylene sorbitan monostearate. At 40°C the ground active substance is homogeneously dispersed in the melt. It is cooled to 10 38°C and poured into slightly chilled suppository moulds.



What is claimed is:

1. A compound of the formula I



5 wherein:

X denotes an oxygen or sulphur atom,

R<sub>1</sub> denotes a hydrogen atom or a prodrug group,

R<sub>2</sub> denotes a carboxy group, a straight-chain or branched C<sub>1-6</sub>-alkoxy-carbonyl group, a C<sub>4-7</sub>-cycloalkoxy-carbonyl or an aryloxycarbonyl group,

a straight-chain or branched C<sub>1-6</sub>-alkoxy-carbonyl group, which is terminally substituted in the alkyl moiety by a phenyl, heteroaryl, carboxy, C<sub>1-3</sub>-alkoxy-carbonyl, aminocarbonyl, C<sub>1-3</sub>-alkylamino-carbonyl or di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl group,

a straight-chain or branched C<sub>2-6</sub>-alkoxy-carbonyl group, which is terminally substituted in the alkyl moiety by a chlorine atom or a hydroxy, C<sub>1-3</sub>-alkoxy, amino, C<sub>1-3</sub>-alkylamino or di-(C<sub>1-3</sub>-alkyl)-amino group,

an aminocarbonyl or methylaminocarbonyl group, an ethylaminocarbonyl group optionally substituted in the 2 position of the ethyl group by a hydroxy or C<sub>1-3</sub>-alkoxy group or, if R<sub>4</sub> does not denote an aminosulphonyl-phenyl or N-(C<sub>1-5</sub>-alkyl)-C<sub>1-3</sub>-alkylaminocarbonyl-phenyl group, it may also denote a di-(C<sub>1-2</sub>-alkyl)-aminocarbonyl group,

R<sub>3</sub> denotes a hydrogen atom, a C<sub>1-6</sub>-alkyl, C<sub>3-7</sub>-cycloalkyl, trifluoromethyl or heteroaryl group,

- 5 a phenyl or naphthyl group, a phenyl or naphthyl group mono- or disubstituted by a fluorine, chlorine, bromine or iodine atom, by a trifluoromethyl, C<sub>1-3</sub>-alkyl or C<sub>1-3</sub>-alkoxy group, whilst in the event of disubstitution the substituents may be identical or different and wherein the abovementioned unsubstituted as well as the mono- and disubstituted phenyl and naphthyl groups may additionally be substituted

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by a hydroxy, hydroxy-C<sub>1-3</sub>-alkyl or C<sub>1-3</sub>-alkoxy-C<sub>1-3</sub>-alkyl group,

by a cyano, carboxy, carboxy-C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-3</sub>-alkylamino-carbonyl or di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl group,

15

by a nitro group,

by an amino, C<sub>1-3</sub>-alkylamino, di-(C<sub>1-3</sub>-alkyl)-amino or amino-C<sub>1-3</sub>-alkyl group,

20

by a C<sub>1-3</sub>-alkylcarbonylamino, N-(C<sub>1-3</sub>-alkyl)-C<sub>1-3</sub>-alkyl-carbonylamino, C<sub>1-3</sub>-alkylcarbonylamino-C<sub>1-3</sub>-alkyl, N-(C<sub>1-3</sub>-alkyl)-

C<sub>1-3</sub>-alkylcarbonylamino-C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkyl-sulphonylamino,

C<sub>1-3</sub>-alkylsulphonylamino-C<sub>1-3</sub>-alkyl, N-(C<sub>1-3</sub>-alkyl)-

C<sub>1-3</sub>-alkylsulphonylamino-C<sub>1-3</sub>-alkyl or aryl-C<sub>1-3</sub>-alkylsulphonylamino group,

25

by a cycloalkylamino, cycloalkyleneimino, cycloalkyleneiminocarbonyl, cycloalkyleneimino-C<sub>1-3</sub>-alkyl, cycloalkyleneiminocarbonyl-C<sub>1-3</sub>-alkyl or cycloalkyleneiminosulphonyl-C<sub>1-3</sub>-alkyl group having 4 to 7 ring members in each case, whilst in each case the methylene group in position 4 of a 6- or 7-membered

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cycloalkyleneimino group may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH or -N(C<sub>1-3</sub>-alkyl) group,

or by a heteroaryl or heteroaryl-C<sub>1-3</sub>-alkyl group,

R<sub>4</sub> denotes a C<sub>3-7</sub>-cycloalkyl group,

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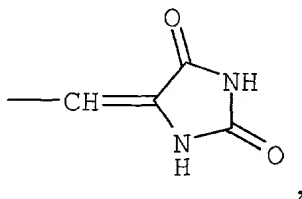
whilst the methylene group in the 4 position of a 6- or 7-membered cycloalkyl group may be substituted by an amino, C<sub>1-3</sub>-alkylamino or di-(C<sub>1-3</sub>-alkyl)-amino group or replaced by an -NH or -N(C<sub>1-3</sub>-alkyl) group,

- 10 or a phenyl group substituted by the group R<sub>6</sub>, which may additionally be mono- or disubstituted by fluorine, chlorine, bromine or iodine atoms, by C<sub>1-5</sub>-alkyl, trifluoromethyl, hydroxy, C<sub>1-3</sub>-alkoxy, carboxy, C<sub>1-3</sub>-alkoxycarbonyl, amino, acetyl amino, C<sub>1-3</sub>-alkyl-sulphonylamino, aminocarbonyl, C<sub>1-3</sub>-alkyl-aminocarbonyl, di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl, aminosulphonyl, C<sub>1-3</sub>-alkyl-aminosulphonyl,
- 15 di-(C<sub>1-3</sub>-alkyl)-aminosulphonyl, nitro or cyano groups, wherein the substituents may be identical or different and wherein

R<sub>6</sub> denotes a hydrogen, fluorine, chlorine, bromine or iodine atom,

- 20 a cyano, nitro, amino, C<sub>1-5</sub>-alkyl, C<sub>3-7</sub>-cycloalkyl, trifluoromethyl, phenyl, tetrazolyl or heteroaryl group,

the group of formula



- 25 wherein the hydrogen atoms bound to a nitrogen atom may in each case be replaced independently of one another by a C<sub>1-3</sub>-alkyl group,

a C<sub>1-3</sub>-alkoxy group, a C<sub>1-3</sub>-alkoxy-C<sub>1-3</sub>-alkoxy, phenyl-C<sub>1-3</sub>-alkoxy, amino-C<sub>2-3</sub>-alkoxy, C<sub>1-3</sub>-alkylamino-C<sub>2-3</sub>-alkoxy, di-(C<sub>1-3</sub>-alkyl)-amino-C<sub>2-3</sub>-alkoxy, phenyl-C<sub>1-3</sub>-alkylamino-C<sub>2-3</sub>-alkoxy, N-(C<sub>1-3</sub>-alkyl)-phenyl-C<sub>1-3</sub>-alkylamino-C<sub>2-3</sub>-alkoxy, C<sub>5-7</sub>-cycloalkyleneimino-C<sub>2-3</sub>-alkoxy or C<sub>1-3</sub>-alkylmercapto group,

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a carboxy, C<sub>1-4</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-3</sub>-alkylamino-carbonyl, N-(C<sub>1-5</sub>-alkyl)-C<sub>1-3</sub>-alkylaminocarbonyl, phenyl-C<sub>1-3</sub>-alkylamino-carbonyl, N-(C<sub>1-3</sub>-alkyl)-phenyl-C<sub>1-3</sub>-alkylamino-carbonyl, piperazinocarbonyl or N-(C<sub>1-3</sub>-alkyl)-piperazinocarbonyl group,

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a C<sub>1-3</sub>-alkylaminocarbonyl or N-(C<sub>1-5</sub>-alkyl)-C<sub>1-3</sub>-alkylaminocarbonyl group wherein an alkyl moiety is substituted by a carboxy or C<sub>1-3</sub>-alkoxycarbonyl group or in the 2 or 3 position by a di-(C<sub>1-3</sub>-alkyl)-amino, piperazino, N-(C<sub>1-3</sub>-alkyl)-piperazino or a 4- to 7-membered cycloalkyleneimino group,

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a C<sub>3-7</sub>-cycloalkyl-carbonyl group,

wherein the methylene group in the 4 position of the 6- or 7-membered cycloalkyl moiety may be substituted by an amino, C<sub>1-3</sub>-alkylamino or di-(C<sub>1-3</sub>-alkyl)-amino group or replaced by an -NH or -N(C<sub>1-3</sub>-alkyl) group,

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a 4- to 7-membered cycloalkyleneimino group wherein

a methylene group linked to the imino group may be replaced by a carbonyl or sulphonyl group or

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the cycloalkylene moiety may be fused to a phenyl ring or

one or two hydrogen atoms may each be replaced by a C<sub>1-3</sub>-alkyl group and/or

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in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be substituted by a carboxy, C<sub>1-3</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-3</sub>-alkylaminocarbonyl, di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl, phenyl-C<sub>1-3</sub>-alkylamino or N-(C<sub>1-3</sub>-alkyl)-phenyl-C<sub>1-3</sub>-alkylamino group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH, -N(C<sub>1-3</sub>-alkyl), -N(phenyl), -N(C<sub>1-3</sub>-alkyl-carbonyl) or -N(benzoyl) group,

a C<sub>1-4</sub>-alkyl group substituted by the group R<sub>7</sub>, wherein

R<sub>7</sub> denotes a C<sub>3-7</sub>-cycloalkyl group,

whilst the methylene group in the 4 position of a 6- or 7-membered cycloalkyl group may be substituted by an amino, C<sub>1-3</sub>-alkylamino or di-(C<sub>1-3</sub>-alkyl)-amino group or replaced by an -NH or -N(C<sub>1-3</sub>-alkyl) group or

in a 5- to 7-membered cycloalkyl group a -(CH<sub>2</sub>)<sub>2</sub> group may be replaced by a -CO-NH group, a -(CH<sub>2</sub>)<sub>3</sub> group may be replaced by a -NH-CO-NH or -CO-NH-CO group or a -(CH<sub>2</sub>)<sub>4</sub> group may be replaced by a -NH-CO-NH-CO group, whilst in each case a hydrogen atom bound to a nitrogen atom may be replaced by a C<sub>1-3</sub>-alkyl group,

an aryl or heteroaryl group,

a hydroxy or C<sub>1-3</sub>-alkoxy group,

an amino, C<sub>1-7</sub>-alkylamino, di-(C<sub>1-7</sub>-alkyl)-amino, phenylamino, N-phenyl-C<sub>1-3</sub>-alkyl-amino, phenyl-C<sub>1-3</sub>-alkylamino, N-(C<sub>1-3</sub>-alkyl)-phenyl-C<sub>1-3</sub>-alkylamino or di-(phenyl-C<sub>1-3</sub>-alkyl)-amino group,

an  $\omega$ -hydroxy-C<sub>2-3</sub>-alkyl-amino, N-(C<sub>1-3</sub>-alkyl)- $\omega$ -hydroxy-C<sub>2-3</sub>-alkyl-amino, di-( $\omega$ -hydroxy-C<sub>2-3</sub>-alkyl)-amino, di-( $\omega$ -(C<sub>1-3</sub>-alkoxy)-C<sub>2-3</sub>-alkyl)-amino or N-(dioxolan-2-yl)-C<sub>1-3</sub>-alkyl-amino group,

5 a C<sub>1-3</sub>-alkylcarbonylamino-C<sub>2-3</sub>-alkyl-amino or C<sub>1-3</sub>-alkylcarbonylamino-C<sub>2-3</sub>-alkyl-N-(C<sub>1-3</sub>-alkyl)-amino group,

a C<sub>1-3</sub>-alkylsulphonylamino, N-(C<sub>1-3</sub>-alkyl)-C<sub>1-3</sub>-alkylsulphonylamino, C<sub>1-3</sub>-alkylsulphonylamino-C<sub>2-3</sub>-alkyl-amino or  
10 C<sub>1-3</sub>-alkylsulphonylamino-C<sub>2-3</sub>-alkyl-N-(C<sub>1-3</sub>-alkyl)-amino group,

a hydroxycarbonyl-C<sub>1-3</sub>-alkylamino or N-(C<sub>1-3</sub>-alkyl)-hydroxycarbonyl-C<sub>1-3</sub>-alkyl-amino group,

15 a guanidino group wherein one or two hydrogen atoms may each be replaced by a C<sub>1-3</sub>-alkyl group,

a group of formula

20 
$$-N(R_8)-CO-(CH_2)_n-R_9 \quad (II),$$

wherein

R<sub>8</sub> denotes a hydrogen atom or a C<sub>1-3</sub>-alkyl group,

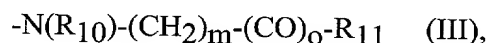
25 n denotes one of the numbers 0, 1, 2 or 3 and

R<sub>9</sub> denotes an amino, C<sub>1-4</sub>-alkylamino, di-(C<sub>1-4</sub>-alkyl)-amino, phenylamino, N-(C<sub>1-4</sub>-alkyl)-phenylamino, benzylamino, N-(C<sub>1-4</sub>-alkyl)-benzylamino or  
30 C<sub>1-4</sub>-alkoxy group, a 4- to 7-membered cycloalkyleneimino group, whilst in each case the methylene group in the 4 position of a 6- or 7-membered

cycloalkyleneimino group may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH, -N(C<sub>1-3</sub>-alkyl), -N(phenyl), -N(C<sub>1-3</sub>-alkyl-carbonyl) or -N(benzoyl) group, or, if n denotes one of the numbers 1, 2 or 3, it may also denote a hydrogen atom,

5

a group of formula



10

wherein

R<sub>10</sub> denotes a hydrogen atom, a C<sub>1-3</sub>-alkyl group, a C<sub>1-3</sub>-alkylcarbonyl, arylcarbonyl, phenyl-C<sub>1-3</sub>-alkyl-carbonyl, C<sub>1-3</sub>-alkylsulphonyl, arylsulphonyl or phenyl-C<sub>1-3</sub>-alkylsulphonyl group,

15

m denotes one of the numbers 1, 2, 3 or 4,

o denotes the number 1 or, if m denotes one of the numbers 2, 3 or 4, o may also denote the number 0 and

20

R<sub>11</sub> denotes an amino, C<sub>1-4</sub>-alkylamino, di-(C<sub>1-4</sub>-alkyl)-amino, phenylamino, N-(C<sub>1-4</sub>-alkyl)-phenylamino, benzylamino, N-(C<sub>1-4</sub>-alkyl)-benzylamino, C<sub>1-4</sub>-alkoxy or C<sub>1-3</sub>-alkoxy-C<sub>1-3</sub>-alkoxy group, a di-(C<sub>1-4</sub>-alkyl)-amino-C<sub>1-3</sub>-alkylamino group optionally substituted in the 1 position by a C<sub>1-3</sub>-alkyl group or a 4- to 7-membered cycloalkyleneimino group, wherein the cycloalkylene moiety may be fused to a phenyl ring or in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH, -N(C<sub>1-3</sub>-alkyl), -N(phenyl), -N(C<sub>1-3</sub>-alkyl-carbonyl) or -N(benzoyl) group,

25

30

a C<sub>4-7</sub>-cycloalkylamino, C<sub>4-7</sub>-cycloalkyl-C<sub>1-3</sub>-alkylamino or C<sub>4-7</sub>-cycloalkenylamino group wherein position 1 of the ring is not involved in the double bond and wherein the abovementioned groups may each additionally be substituted at the amino-nitrogen atom by a C<sub>5-7</sub>-cycloalkyl, C<sub>2-4</sub>-alkenyl or C<sub>1-4</sub>-alkyl group,

5

a 4- to 7-membered cycloalkyleneimino group, wherein

the cycloalkylene moiety may be fused to a phenyl group or to an oxazolo, imidazolo, thiazolo, pyridino, pyrazino or pyrimidino group optionally substituted by a fluorine, chlorine, bromine or iodine atom, by a nitro, C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkoxy or amino group, and/or

10

one or two hydrogen atoms may each be replaced by a C<sub>1-3</sub>-alkyl, C<sub>5-7</sub>-cycloalkyl or phenyl group and/or

15

the methylene group in the 3 position of a 5-membered cycloalkyleneimino group may be substituted by a hydroxy, hydroxy-C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkoxy or C<sub>1-3</sub>-alkoxy-C<sub>1-3</sub>-alkyl group,

20

the methylene group in the 3 or 4 position of a 6- or 7-membered cycloalkyleneimino group may in each case be substituted by a hydroxy, hydroxy-C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkoxy, C<sub>1-3</sub>-alkoxy-C<sub>1-3</sub>-alkyl, carboxy, C<sub>1-4</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-3</sub>-alkylaminocarbonyl, di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl, phenyl-C<sub>1-3</sub>-alkylamino or N-(C<sub>1-3</sub>-alkyl)-phenyl-C<sub>1-3</sub>-alkyl-amino group or

25

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH, -N(C<sub>1-3</sub>-alkyl-), -N(phenyl), -N(phenyl-C<sub>1-3</sub>-alkyl-), -N(C<sub>1-3</sub>-alkyl-carbonyl-), -N(C<sub>1-4</sub>-hydroxy-carbonyl-), -N(C<sub>1-4</sub>-alkoxy-carbonyl-), -N(benzoyl-) or -N(phenyl-C<sub>1-3</sub>-alkyl-carbonyl-) group,

30



wherein a methylene group linked to an imino-nitrogen atom of the cycloalkyleneimino group may be replaced by a carbonyl or sulphonyl group or in a 5- to 7-membered monocyclic cycloalkyleneimino group or a cycloalkyleneimino group fused to a phenyl group the two methylene groups linked to the imino-nitrogen atom may each be replaced by a carbonyl group,

or R<sub>6</sub> denotes a C<sub>1-4</sub>-alkyl group which is substituted by a carboxy, C<sub>1-3</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-3</sub>-alkylaminocarbonyl or di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl group or by a 4- to 7-membered cycloalkyleneiminocarbonyl group,

an N-(C<sub>1-3</sub>-alkyl)-C<sub>2-4</sub>-alkanoylamino group which is additionally substituted in the alkyl moiety by a carboxy or C<sub>1-3</sub>-alkoxycarbonyl group,

a group of formula



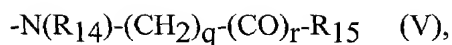
wherein

R<sub>12</sub> denotes a hydrogen atom, a C<sub>1-6</sub>-alkyl or C<sub>3-7</sub>-cycloalkyl group or a C<sub>1-3</sub>-alkyl group terminally substituted by a phenyl, heteroaryl, trifluoromethyl, hydroxy, C<sub>1-3</sub>-alkoxy, aminocarbonyl, C<sub>1-4</sub>-alkylamino-carbonyl, di-(C<sub>1-4</sub>-alkyl)-amino-carbonyl, C<sub>1-3</sub>-alkyl-carbonyl, C<sub>1-3</sub>-alkyl-sulphonylamino, N-(C<sub>1-3</sub>-alkyl)-C<sub>1-3</sub>-alkyl-sulphonylamino, C<sub>1-3</sub>-alkyl-aminosulphonyl or di-(C<sub>1-3</sub>-alkyl)-aminosulphonyl group and

p denotes one of the numbers 0, 1, 2 or 3 and

R<sub>13</sub> assumes the meanings of the abovementioned group R<sub>7</sub>, or, if p denotes one of the numbers 1, 2 or 3, it may also denote a hydrogen atom,

a group of formula



5

wherein

$R_{14}$  denotes a hydrogen atom, a  $C_{1-4}$ -alkyl group, a  $C_{1-3}$ -alkylcarbonyl, arylcarbonyl, phenyl- $C_{1-3}$ -alkylcarbonyl, heteroarylcarbonyl, heteroaryl- $C_{1-3}$ -alkylcarbonyl,  $C_{1-4}$ -alkylsulphonyl, arylsulphonyl, phenyl- $C_{1-3}$ -alkylsulphonyl, heteroarylsulphonyl or heteroaryl- $C_{1-3}$ -alkyl-sulphonyl group,

10

$q$  denotes one of the numbers 1, 2, 3 or 4,

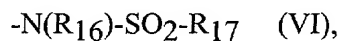
15

$r$  denotes the number 1 or, if  $q$  is one of the numbers 2, 3 or 4, it may also denote the number 0 and

$R_{15}$  assumes the meanings of the abovementioned group  $R_7$ ,

20

a group of formula



wherein

25

$R_{16}$  denotes a hydrogen atom or a  $C_{1-4}$ -alkyl group optionally terminally substituted by a cyano, trifluoromethyl-carbonylamino or  $N$ -( $C_{1-3}$ -alkyl)-trifluoromethyl-carbonyl-amino group and

30

$R_{17}$  denotes a  $C_{1-3}$ -alkyl group,

an amino group substituted by a di-(C<sub>1-3</sub>-alkyl)-amino-C<sub>1-3</sub>-alkyl-carbonyl or di-(C<sub>1-3</sub>-alkyl)-amino-C<sub>1-3</sub>-alkyl-sulphonyl group and a di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl-C<sub>1-3</sub>-alkyl group,

5 or an N-(C<sub>1-3</sub>-alkyl)-C<sub>1-5</sub>-alkylsulphonylamino or N-(C<sub>1-3</sub>-alkyl)-phenylsulphonylamino group wherein the alkyl moiety is additionally substituted by a cyano or carboxy group,

wherein all the single-bonded or fused phenyl groups contained in the groups mentioned under R<sub>6</sub> may be mono- or disubstituted by fluorine, chlorine, bromine or  
10 iodine atoms, by C<sub>1-5</sub>-alkyl, trifluoromethyl, hydroxy, C<sub>1-3</sub>-alkoxy, carboxy, C<sub>1-3</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-4</sub>-alkylamino-carbonyl, di-(C<sub>1-4</sub>-alkyl)-amino-carbonyl, aminosulphonyl, C<sub>1-3</sub>-alkyl-aminosulphonyl, di-(C<sub>1-3</sub>-alkyl)-aminosulphonyl, C<sub>1-3</sub>-alkyl-sulphonylamino, nitro or cyano groups, wherein the substituents may be identical or different, or two adjacent hydrogen  
15 atoms of the phenyl groups may be replaced by a methylenedioxy group,

and

R<sub>5</sub> denotes a hydrogen atom or a C<sub>1-3</sub>-alkyl group,

20 wherein by an aryl group is meant a phenyl or naphthyl group optionally mono- or disubstituted by a fluorine, chlorine, bromine or iodine atom, by a cyano, trifluoromethyl, nitro, carboxy, aminocarbonyl, C<sub>1-3</sub>-alkyl or C<sub>1-3</sub>-alkoxy group and

25 by a heteroaryl group is meant a monocyclic 5- or 6-membered heteroaryl group optionally substituted by a C<sub>1-3</sub>-alkyl group in the carbon skeleton, wherein

the 6-membered heteroaryl group contains one, two or three nitrogen atoms and

30 the 5-membered heteroaryl group contains an imino group optionally substituted by a C<sub>1-3</sub>-alkyl or phenyl-C<sub>1-3</sub>-alkyl group, an oxygen or sulphur atom or

an imino group optionally substituted by a C<sub>1-3</sub>-alkyl or phenyl-C<sub>1-3</sub>-alkyl group or an oxygen or sulphur atom and additionally a nitrogen atom or

5 an imino group optionally substituted by a C<sub>1-3</sub>-alkyl or phenyl-C<sub>1-3</sub>-alkyl group and two nitrogen atoms,

and moreover a phenyl ring may be fused to the abovementioned monocyclic heterocyclic groups via two adjacent carbon atoms and the bonding takes place via a  
10 nitrogen atom or via a carbon atom of the heterocyclic moiety or a fused phenyl ring,

some or all of the hydrogen atoms in the abovementioned alkyl and alkoxy groups or in the alkyl moieties contained in the above-defined groups of formula I may be replaced by fluorine atoms,

15 and the hydrogen atom of any carboxy group present or a hydrogen atom bound to a nitrogen atom may each be replaced by a group which can be cleaved *in vivo*,

or a tautomer or salt thereof.

20

2. A compound of the formula I according to claim 1, wherein:

R<sub>1</sub> and R<sub>3</sub> are as defined in claim 1,

25

X denotes an oxygen atom,

R<sub>2</sub> denotes a carboxy group, a straight-chain or branched C<sub>1-6</sub>-alkoxy-carbonyl group, a C<sub>5-7</sub>-cycloalkoxycarbonyl or a phenoxycarbonyl group,

30

a straight-chain or branched C<sub>1-3</sub>-alkoxy-carbonyl group, which is terminally substituted in the alkyl moiety by a phenyl, heteroaryl, carboxy, C<sub>1-3</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-3</sub>-alkylaminocarbonyl or di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl group,

- 5 a straight-chain or branched C<sub>2-3</sub>-alkoxy-carbonyl group, which is terminally substituted in the alkyl moiety by a chlorine atom, by a hydroxy, C<sub>1-3</sub>-alkoxy, amino, C<sub>1-3</sub>-alkylamino or di-(C<sub>1-3</sub>-alkyl)-amino group,

- an aminocarbonyl or methylaminocarbonyl group, an ethylaminocarbonyl group optionally substituted in the 2 position of the ethyl group by a hydroxy or C<sub>1-3</sub>-alkoxy group or, if R<sub>4</sub> does not denote an aminosulphonyl-phenyl or N-(C<sub>1-5</sub>-alkyl)-C<sub>1-3</sub>-alkylaminocarbonyl-phenyl group, it may also denote a di-(C<sub>1-2</sub>-alkyl)-aminocarbonyl group,
- 10

R<sub>4</sub> denotes a C<sub>3-7</sub>-cycloalkyl group,

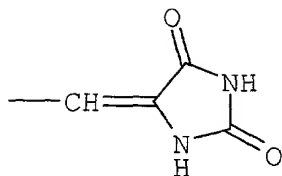
- 15 whilst the methylene group in the 4 position of a 6- or 7-membered cycloalkyl group may be substituted by an amino, C<sub>1-3</sub>-alkylamino or di-(C<sub>1-3</sub>-alkyl)-amino group or replaced by an -NH or -N(C<sub>1-3</sub>-alkyl) group,

- 20 or a phenyl group substituted by the group R<sub>6</sub>, which may additionally be mono- or disubstituted by fluorine, chlorine or bromine atoms, by C<sub>1-3</sub>-alkyl, trifluoromethyl, hydroxy, C<sub>1-3</sub>-alkoxy, carboxy, C<sub>1-3</sub>-alkoxycarbonyl, amino, acetylamino, aminocarbonyl, C<sub>1-3</sub>-alkyl-aminocarbonyl, di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl, nitro or cyano groups, wherein the substituents may be identical or different and wherein

- 25 R<sub>6</sub> denotes a hydrogen, fluorine, chlorine, bromine or iodine atom,

a cyano, nitro, amino, C<sub>1-5</sub>-alkyl, C<sub>3-7</sub>-cycloalkyl, trifluoromethyl, phenyl, tetrazolyl or heteroaryl group,

- 30 the group of formula



wherein a hydrogen atom bound to the nitrogen atom may be replaced by a C<sub>1-3</sub>-alkyl group,

5 a C<sub>1-3</sub>-alkoxy group, an amino-C<sub>2-3</sub>-alkoxy, C<sub>1-3</sub>-alkylamino-C<sub>2-3</sub>-alkoxy, di-(C<sub>1-3</sub>-alkyl)-amino-C<sub>2-3</sub>-alkoxy, phenyl-C<sub>1-3</sub>-alkylamino-C<sub>2-3</sub>-alkoxy, N-(C<sub>1-3</sub>-alkyl)-phenyl-C<sub>1-3</sub>-alkylamino-C<sub>2-3</sub>-alkoxy, pyrrolidino-C<sub>2-3</sub>-alkoxy, piperidino-C<sub>2-3</sub>-alkoxy or C<sub>1-3</sub>-alkylmercapto group,

10 a carboxy, C<sub>1-4</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-3</sub>-alkylamino-carbonyl, phenyl-C<sub>1-3</sub>-alkylamino-carbonyl or N-(C<sub>1-3</sub>-alkyl)-phenyl-C<sub>1-3</sub>-alkylamino-carbonyl group,

a C<sub>3-7</sub>-cycloalkyl-carbonyl group,

15 wherein the methylene group in the 4 position of the 6- or 7-membered cycloalkyl moiety may be replaced by an -NH or -N(C<sub>1-3</sub>-alkyl) group,

a 4- to 7-membered cycloalkyleneimino group, wherein

20 a methylene group linked to the imino group may be replaced by a carbonyl or sulphonyl group or

one or two hydrogen atoms may each be replaced by a C<sub>1-3</sub>-alkyl group and/or

25 in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be substituted by a carboxy, C<sub>1-3</sub>-alkoxycarbonyl,

aminocarbonyl, C<sub>1-3</sub>-alkylaminocarbonyl, di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl,  
phenyl-C<sub>1-3</sub>-alkylamino or N-(C<sub>1-3</sub>-alkyl)-phenyl-C<sub>1-3</sub>-alkylamino group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH or  
-N(C<sub>1-3</sub>-alkyl) group,

a C<sub>1-4</sub>-alkyl group terminally substituted by the group R<sub>7</sub>, wherein

R<sub>7</sub> denotes a C<sub>5-7</sub>-cycloalkyl group,

whilst the methylene group in the 4 position of a 6- or 7-membered cycloalkyl  
group may be replaced by an -NH or -N(C<sub>1-3</sub>-alkyl) group or

in a 5- to 7-membered cycloalkyl group a -(CH<sub>2</sub>)<sub>2</sub> group may be replaced by a  
-CO-NH group, a -(CH<sub>2</sub>)<sub>3</sub> group may be replaced by a -NH-CO-NH- or a  
-(CH<sub>2</sub>)<sub>4</sub> group may be replaced by a -NH-CO-NH-CO group, whilst in each case  
a hydrogen atom bound to a nitrogen atom may be replaced by a C<sub>1-3</sub>-alkyl  
group,

a phenyl or heteroaryl group,

a hydroxy or C<sub>1-3</sub>-alkoxy group,

an amino, C<sub>1-6</sub>-alkylamino, di-(C<sub>1-6</sub>-alkyl)-amino, phenylamino, N-phenyl-C<sub>1-3</sub>-alkyl-  
amino, phenyl-C<sub>1-3</sub>-alkylamino, N-(C<sub>1-3</sub>-alkyl)-phenyl-C<sub>1-3</sub>-alkylamino or di-(phenyl-  
C<sub>1-3</sub>-alkyl)-amino group,

a ω-hydroxy-C<sub>2-3</sub>-alkyl-amino, N-(C<sub>1-3</sub>-alkyl)-ω-hydroxy-C<sub>2-3</sub>-alkyl-amino,  
di-(ω-hydroxy-C<sub>2-3</sub>-alkyl)-amino, di-(ω-(C<sub>1-3</sub>-alkoxy)-C<sub>2-3</sub>-alkyl)-amino or  
N-(dioxolan-2-yl)-C<sub>1-3</sub>-alkyl-amino group,

a C<sub>1-3</sub>-alkylcarbonylamino-C<sub>2-3</sub>-alkyl-amino or  
C<sub>1-3</sub>-alkylcarbonylamino-C<sub>2-3</sub>-alkyl-N-(C<sub>1-3</sub>-alkyl)-amino group,

a C<sub>1-3</sub>-alkylsulphonylamino, N-(C<sub>1-3</sub>-alkyl)-C<sub>1-3</sub>-alkylsulphonylamino,  
C<sub>1-3</sub>-alkylsulphonylamino--C<sub>2-3</sub>-alkyl-amino or C<sub>1-3</sub>-alkylsulphonylamino-C<sub>2-3</sub>-alkyl-  
-N-(C<sub>1-3</sub>-alkyl)-amino group,

a hydroxycarbonyl-C<sub>1-3</sub>-alkylamino or  
N-(C<sub>1-3</sub>-alkyl)-hydroxycarbonyl-C<sub>1-3</sub>-alkyl-amino group

a guanidino group wherein a hydrogen atom may be replaced by a C<sub>1-3</sub>-alkyl group,

a group of formula



wherein

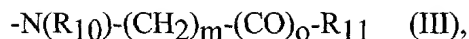
R<sub>8</sub> denotes a hydrogen atom or a C<sub>1-3</sub>-alkyl group,

n denotes one of the numbers 0, 1, 2 or 3 and

R<sub>9</sub> denotes an amino, C<sub>1-3</sub>-alkylamino, di-(C<sub>1-3</sub>-alkyl)-amino, phenylamino,  
benzylamino or C<sub>1-4</sub>-alkoxy group, a 5- to 7-membered cycloalkyleneimino  
group, wherein the methylene group in position 4 of the piperidino group may be  
replaced by an oxygen or sulphur atom, by an -NH, -N(C<sub>1-3</sub>-alkyl), -N(phenyl),  
-N(C<sub>1-3</sub>-alkyl-carbonyl) or -N(benzoyl) group, or, if n denotes one of the  
numbers 1, 2 or 3, it may also denote a hydrogen atom,

a group of formula





wherein

5             $\text{R}_{10}$  denotes a hydrogen atom, a  $\text{C}_{1-3}$ -alkyl group, a  $\text{C}_{1-3}$ -alkylcarbonyl or  $\text{C}_{1-3}$ -alkylsulphonyl group,

$m$  denotes one of the numbers 1, 2 or 3,

10            $o$  denotes the number 1 or, if  $m$  is one of the numbers 2 or 3,  $o$  may also denote the number 0 and

$\text{R}_{11}$  denotes an amino,  $\text{C}_{1-3}$ -alkylamino, di- $(\text{C}_{1-3}$ -alkyl)-amino,  $\text{C}_{1-4}$ -alkoxy or  $\text{C}_{1-3}$ -alkoxy- $\text{C}_{1-3}$ -alkoxy group or a 5- to 7-membered cycloalkyleneimino group,  
15           wherein the methylene group in position 4 of the piperidino group may be replaced by an oxygen or sulphur atom, by an  $-\text{NH}$ ,  $-\text{N}(\text{C}_{1-3}\text{-alkyl})$ ,  $-\text{N}(\text{phenyl})$ ,  $-\text{N}(\text{C}_{1-3}\text{-alkyl-carbonyl})$  or  $-\text{N}(\text{benzoyl})$  group,

a  $\text{C}_{4-7}$ -cycloalkylamino or  $\text{C}_{4-7}$ -cycloalkenylamino group wherein position 1 of the  
20           ring is not involved in the double bond,

a 4- to 7-membered cycloalkyleneimino group, wherein

25           the cycloalkylene moiety may be fused to a phenyl group or

one or two hydrogen atoms may each be replaced by a  $\text{C}_{1-3}$ -alkyl group and/or

the methylene group in position 3 of the pyrrolidino group may be substituted by  
a hydroxy or  $\text{C}_{1-3}$ -alkoxy group,

30

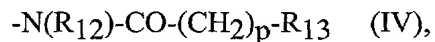
in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be substituted by a hydroxy, hydroxy-C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkoxy, carboxy, C<sub>1-3</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-3</sub>-alkylamino-carbonyl, di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl, phenyl-C<sub>1-3</sub>-alkylamino or  
 5 N-(C<sub>1-3</sub>-alkyl)-phenyl-C<sub>1-3</sub>-alkylamino group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH, -N(C<sub>1-3</sub>-alkyl), -N(phenyl), -N(phenyl-C<sub>1-3</sub>-alkyl), -N(C<sub>1-3</sub>-alkyl-carbonyl), -N(C<sub>1-4</sub>-alkoxy-carbonyl), -N(benzoyl) or -N(phenyl-C<sub>1-3</sub>-alkyl-carbonyl) group,  
 10

wherein a methylene group linked to an imino-nitrogen atom of the cycloalkyleneimino group may be replaced by a carbonyl or sulphonyl group or in a 5- to 6-membered monocyclic cycloalkyleneimino group or a cycloalkyleneimino group fused to a phenyl group the two methylene  
 15 groups linked to the imino-nitrogen atom may each be replaced by a carbonyl group,

or R<sub>6</sub> denotes a C<sub>1-4</sub>-alkyl group which is terminally substituted by a carboxy, C<sub>1-3</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-3</sub>-alkylaminocarbonyl or  
 20 di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl group or by a 4- to 7-membered cycloalkyleneiminocarbonyl group,

a group of formula



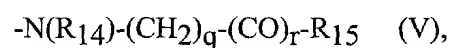
wherein

30 R<sub>12</sub> denotes a hydrogen atom, a C<sub>1-3</sub>-alkyl, C<sub>5-7</sub>-cycloalkyl, phenyl-C<sub>1-3</sub>-alkyl or heteroaryl-C<sub>1-3</sub>-alkyl group and

p denotes one of the numbers 0, 1, 2 or 3 and

R<sub>13</sub> assumes the meanings of the abovementioned group R<sub>7</sub>, or, if p denotes one of  
5 the numbers 1, 2 or 3, it may also denote a hydrogen atom,

a group of formula



10

wherein

R<sub>14</sub> denotes a hydrogen atom, a C<sub>1-4</sub>-alkyl group, a C<sub>1-3</sub>-alkylcarbonyl,  
phenylcarbonyl, phenyl-C<sub>1-3</sub>-alkylcarbonyl, heteroarylcarbonyl,  
15 heteroaryl-C<sub>1-3</sub>-alkylcarbonyl, C<sub>1-4</sub>-alkylsulphonyl, phenylsulphonyl,  
phenyl-C<sub>1-3</sub>-alkylsulphonyl- heteroarylsulphonyl or heteroaryl-C<sub>1-3</sub>-alkyl-sulphonyl  
group,

q denotes one of the numbers 1, 2, 3 or 4,

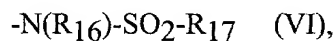
20

r denotes the number 1 or, if q is one of the numbers 2, 3 or 4, it may also denote the  
number 0 and

R<sub>15</sub> assumes the meanings of the abovementioned group R<sub>7</sub>,

25

a group of formula



wherein

30

R<sub>16</sub> denotes a hydrogen atom or a C<sub>1-4</sub>-alkyl group optionally terminally substituted by a cyano, trifluoromethyl-carbonylamino or N-(C<sub>1-3</sub>-alkyl)-trifluoromethyl-carbonyl-amino group and

5 R<sub>17</sub> denotes a C<sub>1-3</sub>-alkyl group,

an amino group substituted by a di-(C<sub>1-3</sub>-alkyl)-amino-C<sub>1-3</sub>-alkyl-carbonyl or di-(C<sub>1-3</sub>-alkyl)-amino-C<sub>1-3</sub>-alkyl-sulphonyl group and a di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl-C<sub>1-3</sub>-alkyl group,

10

wherein all the single-bonded or fused phenyl groups contained in the groups mentioned under R<sub>6</sub> may be mono- or disubstituted by fluorine, chlorine or bromine atoms, by C<sub>1-3</sub>-alkyl, trifluoromethyl, hydroxy, C<sub>1-3</sub>-alkoxy, carboxy, C<sub>1-3</sub>-alkoxycarbonyl, aminocarbonyl, C<sub>1-3</sub>-alkyl-aminocarbonyl, 15 aminosulphonyl, C<sub>1-3</sub>-alkyl-aminosulphonyl, nitro or cyano groups, wherein the substituents may be identical or different, or two adjacent hydrogen atoms of the phenyl groups may be replaced by a methylenedioxy group, and

15

R<sub>5</sub> denotes a hydrogen atom or a C<sub>1-3</sub>-alkyl group,

20

whilst by a heteroaryl group as mentioned above is meant a pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, furyl, thienyl, oxazolyl, thiazolyl, pyrazolyl, imidazolyl or triazolyl group optionally substituted in the carbon skeleton by a C<sub>1-3</sub>-alkyl group wherein a hydrogen atom bound to a nitrogen atom may be replaced by a C<sub>1-3</sub>-alkyl or 25 phenyl-C<sub>1-3</sub>-alkyl group and wherein the 5-membered heteroaryl groups containing at least one imino group are bound via a carbon or nitrogen atom,

25

a hydrogen atom bound to a nitrogen atom in the abovementioned groups may be replaced by a group which can be cleaved *in vivo*,

30

the carboxy groups contained in the abovementioned groups may each be substituted by a group which can be cleaved *in vivo*,

some or all of the hydrogen atoms in the abovementioned alkyl and alkoxy groups or in the  
5 alkyl moieties contained in the above-defined groups of formula I may be replaced by  
fluorine atoms and

or a tautomer or salt thereof.

10

3. A compound of the formula I according to claim 1, wherein:

X denotes an oxygen atom,

15 R<sub>1</sub> denotes a hydrogen atom,

R<sub>2</sub> denotes a carboxy group, a straight-chain or branched C<sub>1-4</sub>-alkoxycarbonyl group or a  
phenoxycarbonyl group,

20 a straight-chain or branched C<sub>1-3</sub>-alkoxy-carbonyl group, which is terminally substituted in  
the alkyl moiety by a phenyl, carboxy, C<sub>1-3</sub>-alkoxycarbonyl, aminocarbonyl,  
C<sub>1-3</sub>-alkylaminocarbonyl or di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl group,

a straight-chain or branched C<sub>2-3</sub>-alkoxy-carbonyl group which is terminally substituted in  
25 the alkyl moiety by a hydroxy, C<sub>1-3</sub>-alkoxy, amino, C<sub>1-3</sub>-alkylamino or  
di-(C<sub>1-3</sub>-alkyl)-amino group,

an aminocarbonyl or methylaminocarbonyl group, an ethylaminocarbonyl group optionally  
substituted in the 2 position of the ethyl group by a hydroxy or C<sub>1-3</sub>-alkoxy group or, if R<sub>4</sub>  
30 does not denote an aminosulphonyl-phenyl or N-(C<sub>1-5</sub>-alkyl)-C<sub>1-3</sub>-alkylaminocarbonyl-  
phenyl group, it may also denote a di-(C<sub>1-2</sub>-alkyl)-aminocarbonyl group,

R<sub>3</sub> denotes a C<sub>1-4</sub>-alkyl group or a phenyl group which may be substituted by a fluorine, chlorine or bromine atom, by a trifluoromethyl, C<sub>1-3</sub>-alkyl, hydroxy or C<sub>1-3</sub>-alkoxy group,

5

R<sub>4</sub> denotes a C<sub>5-6</sub>-cycloalkyl group,

wherein the methylene group in position 4 of the cyclohexyl group may be substituted by an amino, C<sub>1-3</sub>-alkylamino or di-(C<sub>1-3</sub>-alkyl)-amino group or replaced by an -NH or -N(C<sub>1-3</sub>-alkyl) group,

10

a phenyl group, a phenyl group disubstituted by C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkoxy or nitro groups, wherein the substituents may be identical or different, or

15 a phenyl group substituted by the group R<sub>6</sub>, which may additionally be substituted by a fluorine, chlorine or bromine atom or by an amino or nitro group, wherein

R<sub>6</sub> denotes a fluorine, chlorine or bromine atom,

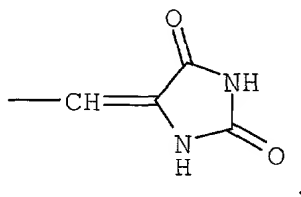
a C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkoxy, nitro, amino or C<sub>5-6</sub>-cycloalkyl group,

20

a pyrrolyl, pyrazolyl, imidazolyl, triazolyl or tetrazolyl group bound via a carbon atom, wherein the abovementioned heteroaromatic groups in the carbon skeleton may be substituted by a C<sub>1-3</sub>-alkyl group or a hydrogen atom bound to a nitrogen atom may be replaced by a C<sub>1-3</sub>-alkyl or phenyl-C<sub>1-3</sub>-alkyl group,

25

the group of formula



a carboxy, C<sub>1-4</sub>-alkoxycarbonyl, phenyl-C<sub>1-3</sub>-alkylamino-carbonyl or C<sub>5-7</sub>-cycloalkyl-carbonyl group,

a 5 or 6-membered cycloalkyleneimino group, wherein

the methylene group in position 4 of the piperidino group may be replaced by an oxygen or sulphur atom, by an -NH or -N(C<sub>1-3</sub>-alkyl) group,

an unbranched C<sub>1-3</sub>-alkyl group terminally substituted by the group R<sub>7</sub>, wherein

R<sub>7</sub> denotes a C<sub>5-7</sub>-cycloalkyl group,

wherein in a 5 or 6-membered cycloalkyl group a -(CH<sub>2</sub>)<sub>2</sub> group may be replaced by a -CO-NH group, a -(CH<sub>2</sub>)<sub>3</sub> group may be replaced by an -NH-CO-NH- or a -(CH<sub>2</sub>)<sub>4</sub> group may be replaced by an -NH-CO-NH-CO group, whilst in each case a hydrogen atom bound to a nitrogen atom may be replaced by a C<sub>1-3</sub>-alkyl group,

a phenyl or pyridinyl group or a pyrrolyl, pyrazolyl, imidazolyl or triazolyl group bound via a carbon or nitrogen atom, wherein the abovementioned heteroaromatic groups in the carbon skeleton may be substituted by a C<sub>1-3</sub>-alkyl group or a hydrogen atom bound to a nitrogen atom may be replaced by a C<sub>1-3</sub>-alkyl group,

a hydroxy or C<sub>1-3</sub>-alkoxy group,

an amino, C<sub>1-6</sub>-alkylamino, di-(C<sub>1-6</sub>-alkyl)-amino, phenylamino, N-phenyl-C<sub>1-3</sub>-alkylamino, phenyl-C<sub>1-3</sub>-alkylamino or N-(C<sub>1-3</sub>-alkyl)-phenyl-C<sub>1-3</sub>-alkylamino group,

a ω-hydroxy-C<sub>2-3</sub>-alkyl-amino, N-(C<sub>1-3</sub>-alkyl)-ω-hydroxy-C<sub>2-3</sub>-alkylamino, di-(ω-hydroxy-C<sub>2-3</sub>-alkyl)-amino or di-(ω-(C<sub>1-3</sub>-alkoxy)-C<sub>2-3</sub>-alkyl)-amino group,

a C<sub>1-3</sub>-alkylcarbonylamino-C<sub>2-3</sub>-alkyl-amino or  
C<sub>1-3</sub>-alkylcarbonylamino-C<sub>2-3</sub>-alkyl-N-(C<sub>1-3</sub>-alkyl)-amino group,

5 a C<sub>1-3</sub>-alkylsulphonylamino, N-(C<sub>1-3</sub>-alkyl)-C<sub>1-3</sub>-alkylsulphonylamino,  
C<sub>1-3</sub>-alkylsulphonylamino--C<sub>2-3</sub>-alkylamino or C<sub>1-3</sub>-alkylsulphonylamino-  
-C<sub>2-3</sub>-alkyl-N-(C<sub>1-3</sub>-alkyl)-amino group,

10 a hydroxycarbonyl-C<sub>1-3</sub>-alkylamino or  
N-(C<sub>1-3</sub>-alkyl)-hydroxycarbonyl-C<sub>1-3</sub>-alkyl-amino group,

a guanidino group wherein a hydrogen atom may be replaced by a C<sub>1-3</sub>-alkyl group,

15 a group of formula



wherein

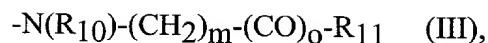
20 R<sub>8</sub> denotes a hydrogen atom or a C<sub>1-3</sub>-alkyl group,

n denotes one of the numbers 0, 1, 2 or 3 and

25 R<sub>9</sub> denotes an amino, C<sub>1-3</sub>-alkylamino, di-(C<sub>1-3</sub>-alkyl)-amino or C<sub>1-4</sub>-alkoxy  
group, a 5- or 6-membered cycloalkyleneimino group, wherein the methylene  
group in position 4 of the piperidino group may be replaced by an -NH,  
-N(C<sub>1-3</sub>-alkyl) or -N(C<sub>1-3</sub>-alkyl-carbonyl) group, or, if n denotes one of the  
numbers 1, 2 or 3, R<sub>9</sub> may also denote a hydrogen atom,

30 a group of formula





wherein

5  $R_{10}$  denotes a hydrogen atom or a  $C_{1-3}$ -alkyl group,

$m$  denotes one of the numbers 1, 2 or 3,

10  $o$  denotes the number 1 or, if  $m$  is one of the numbers 2 or 3,  $o$  may also denote the number 0 and

$R_{11}$  denotes an amino,  $C_{1-3}$ -alkylamino, di- $(C_{1-3}$ -alkyl)-amino,  $C_{1-4}$ -alkoxy or methoxy- $C_{1-3}$ -alkoxy group or a 5- or 6-membered cycloalkyleneimino group, wherein the methylene group in position 4 of the piperidino group may be  
15 replaced by an -NH, -N( $C_{1-3}$ -alkyl) or -N( $C_{1-3}$ -alkyl-carbonyl) group,

an azetidino, pyrrolidino, piperidino, 2,6-dimethyl-piperidino, 3,5-dimethyl-piperidino or azepino group, wherein

20 the methylene group in position 3 of the pyrrolidino group may be substituted by a hydroxy group,

the methylene group in position 4 of the piperidino group may be substituted by a hydroxy, hydroxy- $C_{1-3}$ -alkyl or  $C_{1-3}$ -alkoxy group or

25 may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, -NH, -N( $C_{1-3}$ -alkyl), -N( $C_{1-3}$ -alkyl-carbonyl), -N(benzoyl) or -N(phenyl- $C_{1-3}$ -alkyl-carbonyl) group,

wherein a methylene group linked to an imino-nitrogen atom of the pyrrolidino, piperidino or piperazino group may be replaced by a carbonyl group,

5 or R<sub>6</sub> denotes a straight-chain C<sub>1-3</sub>-alkyl group which is terminally substituted by a carboxy or C<sub>1-3</sub>-alkoxy-carbonyl group,

a group of formula

10 
$$-N(R_{12})-CO-(CH_2)_p-R_{13} \quad (IV),$$

wherein

R<sub>12</sub> denotes a hydrogen atom, a C<sub>1-3</sub>-alkyl or phenyl-C<sub>1-3</sub>-alkyl group,

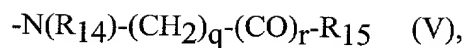
15 p denotes one of the numbers 0, 1 or 2 and

R<sub>13</sub> denotes an amino, C<sub>1-4</sub>-alkylamino, di-(C<sub>1-4</sub>-alkyl)-amino, benzylamino, N-(C<sub>1-3</sub>-alkyl)-benzylamino, C<sub>1-3</sub>-alkoxy-C<sub>1-3</sub>-alkylamino, N-(C<sub>1-3</sub>-alkyl)-C<sub>1-3</sub>-alkoxy-C<sub>1-3</sub>-alkylamino, di-(2-methoxy-ethyl)-amino, di-(ω-hydroxy-C<sub>2-3</sub>-alkyl)-amino or aminocarbonyl-methyl-N-(methyl)-amino group,

20 a pyrrolyl, pyrazolyl or imidazolyl group bound via a nitrogen atom and optionally substituted by a C<sub>1-3</sub>-alkyl group,

25 a pyrrolidino, piperidino, morpholino, thiomorpholino or a piperazino group optionally substituted in the 4 position by a C<sub>1-3</sub>-alkyl, phenyl-C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkylcarbonyl or C<sub>1-4</sub>-alkoxycarbonyl group or, if n denotes the number 1 or 2, it may also denote a hydrogen atom,

30 a group of formula



wherein

5

$\text{R}_{14}$  denotes a hydrogen atom, a  $\text{C}_{1-4}$ -alkyl,  $\text{C}_{1-3}$ -alkyl-carbonyl, phenylcarbonyl, phenyl- $\text{C}_{1-3}$ -alkylcarbonyl, furyl-carbonyl, pyridinyl-carbonyl, furyl- $\text{C}_{1-3}$ -alkyl-carbonyl, pyridinyl- $\text{C}_{1-3}$ -alkylcarbonyl,  $\text{C}_{1-4}$ -alkylsulphonyl, phenylsulphonyl or phenyl- $\text{C}_{1-3}$ -alkylsulphonyl group,

10

$q$  denotes one of the numbers 1, 2 or 3,

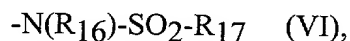
$r$  denotes the number 1 or, if  $q$  is one of the numbers 2 or 3, it may also denote the number 0 and

15

$\text{R}_{15}$  denotes an amino,  $\text{C}_{1-4}$ -alkylamino, di- $(\text{C}_{1-4}$ -alkyl)-amino, phenylamino, N- $(\text{C}_{1-4}$ -alkyl)-phenylamino, benzylamino or N- $(\text{C}_{1-4}$ -alkyl)-benzylamino group,

or a group of formula

20



wherein

$\text{R}_{16}$  denotes a hydrogen atom or a  $\text{C}_{1-3}$ -alkyl group optionally terminally substituted  
by a cyano, trifluoromethyl-carbonylamino or  
N- $(\text{C}_{1-3}$ -alkyl)-trifluoromethyl-carbonyl-amino group and

25

$\text{R}_{17}$  denotes a  $\text{C}_{1-3}$ -alkyl group,

wherein all the single-bonded or fused phenyl groups contained in the groups mentioned under R<sub>6</sub> may be substituted by a fluorine, chlorine or bromine atom, by a methyl, trifluoromethyl, methoxy, nitro or cyano group and

5 R<sub>5</sub> denotes a hydrogen atom,

wherein a hydrogen atom bound to a nitrogen atom in the abovementioned groups may be replaced by an acetyl or tert.butoxycarbonyl group,

10 the carboxy groups contained in the abovementioned groups may also be present in the form of the tert.butoxycarbonyl precursor group,

or a tautomer or salt thereof.

15

4. A compound of the formula I according to claim 1, wherein:

X denotes an oxygen atom,

20 R<sub>1</sub> and R<sub>5</sub> each denote a hydrogen atom,

R<sub>2</sub> denotes a methoxycarbonyl, ethoxycarbonyl or aminocarbonyl group,

R<sub>3</sub> denotes a phenyl group and

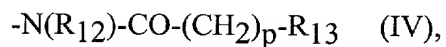
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R<sub>4</sub> denotes a phenyl group monosubstituted by the group R<sub>6</sub>, wherein

R<sub>6</sub> denotes an N-methyl-imidazol-2-yl group,

30 an unbranched C<sub>1-3</sub>-alkyl group which is terminally substituted by a C<sub>1-4</sub>-alkylamino, di-(C<sub>1-4</sub>-alkyl)-amino, piperidino or 2,6-dimethyl-piperidino group,

a group of formula



5

wherein

$\text{R}_{12}$  denotes a  $\text{C}_{1-3}$ -alkyl group,

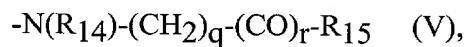
10

$p$  denotes one of the numbers 1 or 2 and

$\text{R}_{13}$  denotes a di- $(\text{C}_{1-3}$ -alkyl)-amino group,

or a group of formula

15



wherein

20

$\text{R}_{14}$  denotes a  $\text{C}_{1-3}$ -alkyl-carbonyl or  $\text{C}_{1-3}$ -alkylsulphonyl group,

$q$  denotes one of the numbers 1, 2 or 3,

$r$  denotes the number 1 or, if  $q$  is one of the numbers 2 or 3,  $r$  may also denote the  
25 number 0 and

$\text{R}_{15}$  denotes a di- $(\text{C}_{1-3}$ -alkyl)-amino group,

or a tautomer or salt thereof.

30

5. A compound selected from the group consisting of:

(a) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

5

(b) 3-Z-[(1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone,

(c) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

10

(d) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

(e) 3-Z-[1-(4-((2,6-dimethyl-piperidin-1-yl)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

15

(f) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

20

(g) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

(h) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

25

(i) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(j) 3-Z-[1-(4-(N-acetyl-N-dimethylaminocarbonylmethyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

30

(k) 3-Z-[1-(4-ethylaminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

5 (l) 3-Z-[1-(4-(1-methyl-imidazol-2-yl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(m) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

10

(n) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(o) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

15

(p) 3-Z-[1-(4-(N-dimethylaminocarbonylmethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

20 (q) 3-Z-[1-(4-(N-((2-dimethylamino-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(r) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone and

25

(s) 3-Z-[1-(4-methylaminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

or a tautomer or salt thereof.

30

6. A physiologically acceptable salt of a compound according to claim 1, 2, 3, 4 or 5.

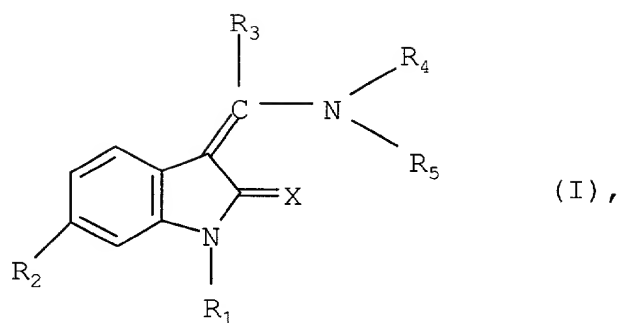
7. A pharmaceutical composition containing a compound according to claim 1, 2, 3 or  
5 4, or a physiologically acceptable salt thereof in accordance with claim 5, together with a  
pharmaceutically acceptable carrier.

8. A method for treating excessive or anomalous cell proliferation which comprises  
10 administering to a host in need of such treatment an antiproliferative amount of a  
compound in accordance with claim 1, 2, 3 or 4, or a physiologically acceptable salt  
thereof in accordance with claim 5.



# Abstract

## 5 Indolinones of the formula



having an inhibitory effect on receptor tyrosine kinases and cyclin/CDK complexes, as

10 well as on the proliferation of endothelial cells and various tumour cells. Exemplary are:  
(a) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

(b) 3-Z-[(1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone, and

15 (c) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone.